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(73) Proprietor: **TAKEDA CHEMICAL INDUSTRIES, LTD.**
3-6, Doshomachi 2-chome Chuo-ku
Osaka (JP)

(72) Inventor: **Meguro, Kanji**
2-21, Mondosou
Nishinomiya-shi Hyogo 662 (JP)
Inventor: **Fujita, Takeshi**
13-15, Nagaodai 1-chome
Takarazuka-shi Hyogo 665 (JP)

(74) Representative: **Lewin, John Harvey et al**
ELKINGTON AND FIFE Beacon House 113
Kingsway
London WC2B 6PP (GB)

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Courier Press, Leamington Spa, England.

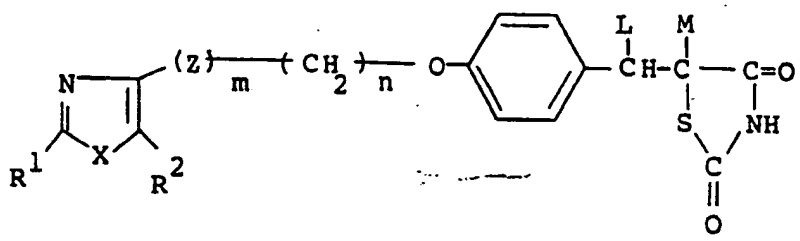
Description

This invention relates to novel thiaz lidinedione derivatives which possess blood-glucose and bl od-lipid lowering actions, to processes for producing the same and to pharmaceutical compositions containing the same.

As a therapeutic agent for diabetes, heretofore, there have been used various biguanide and sulfonylurea compounds. However, the biguanide compounds are hardly in current use, because they cause lactic acid acidosis, while the sulfonylurea compounds exhibit potent hypoglycemic action but often bring about severe hypoglycemia, thus requiring careful precautions on the occasion of their use. The development of a novel therapeutic agent for diabetes which is free from such defects is desired. In Japanese Unexamined Patent Publication Nos. 22636/1980 (EP—A—8203) and 64586/1980, Chemical & Pharmaceutical Bulletin, *30,* 3563 (1982), *ibid., 30,* 3580 (1982) and *ibid., 32,* 2267 (1984), on the other hand, there have been described the facts that various thiazolidinediones exhibit blood-lipid and blood-glucose lowering actions, and in Diabetes, *32,* 804 (1983), furthermore, there has been provided a description of the antidiabetic action demonstrated by ciglitazone. Nevertheless, any of these compounds has failed so far to be commercialized as a therapeutic agent for diabetes. The present inventors conducted repeated research on thiazolidinediones, and as a result, found out entirely novel derivatives which possess outstandingly potent blood-glucose and blood-lipid lowering actions and can be expected to provide enhanced therapeutic effect, as compared with the known compounds.

This invention is concerned with:

1. A thiazolidinedione derivative of the general formula:



(I)

wherein

R^1 is hydrogen,

a hydrocarbon residue having 1 to 13 carbon atoms, or a five- or six-membered ring containing, in addition to carbon, 1 to 3 atoms selected from N, O and S as a ring-forming atom and capable of bonding through carbon, and each of said hydrocarbon residue and said ring may be substituted by 1 to 3 substituents selected from alkyl having 1 to 3 carbon atoms when R^1 includes an alicyclic group or is a saturated heterocyclic group, or by 1 to 4 substituents selected from halogen, hydroxyl, cyano, trifluoromethyl, alkoxy having 1 to 4 carbon atoms, alkyl having 1 to 4 carbon atoms, alkoxycarbonyl having 2 to 4 carbon atoms and alkylthio having 1 to 3 carbon atoms when either R^1 includes aromatic hydrocarbon or R^1 is a heteroaromatic ring group;

R^2 is hydrogen or lower alkyl having 1 to 5 carbon atoms which may be substituted by hydroxyl;

X is an oxygen or sulfur atom;

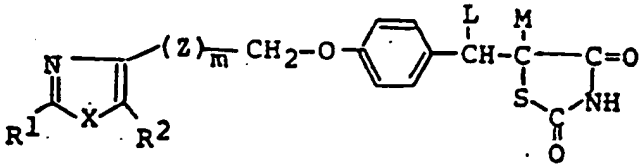
Z is a hydroxylated methylene or carbonyl; m is 0 or 1;

n is an integer of 1 to 3;

L and M represent independently a hydrogen atom or L and M combine with each other to cooperate jointly to form a linkage, or a pharmaceutically acceptable salt thereof.

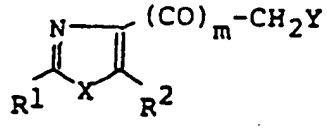
2. A pharmaceutical composition which contains a compound of the general formula (I) or its salt.

3. A process for producing a compound of the general formula:



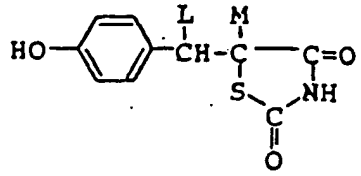
(I-1)

[wherein each of the symbols is as defined hereinbefore] or its salt, which comprises r acting a compound f the general formula:



(II)

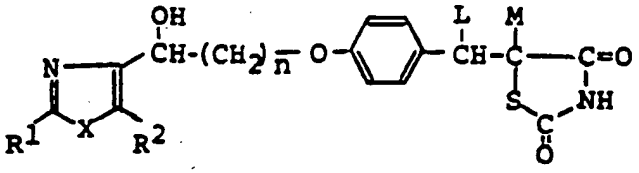
[wherein R^1, R^2, X and m are as defined hereinbefore; Y is a halogen atom] with a compound of the general formula:



(III)

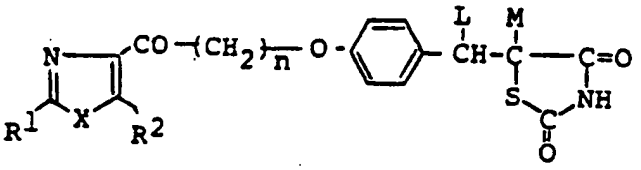
[wherein each of the symbols is as defined hereinbefore] or its salt, followed by reduction of the reaction product, if desired.

4. A process for producing a compound of the general formula:



(I-3)

[wherein each of the symbols is as defined hereinbefore] or its salt, which comprises reducing a compound of the general formula:

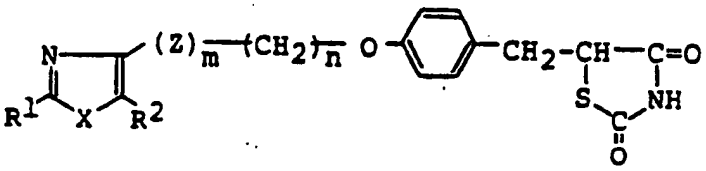


(I-2)

[wherein each of the symbols is as defined hereinbefore] or its salt,

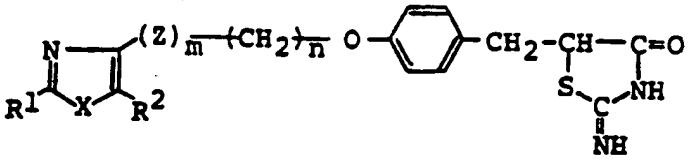
5. A process for producing a compound of the general formula (I-2) or its salt, which comprises oxidizing a compound of the general formula (I-3) or its salt,

6. A process for producing a compound of the general formula:



(I-4)

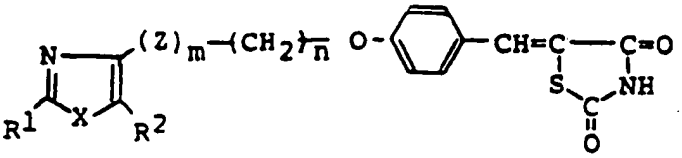
[wherein each of the symbols is as defined hereinbefore] or its salt, which comprises hydrolyzing a compound of the general formula:



(IV)

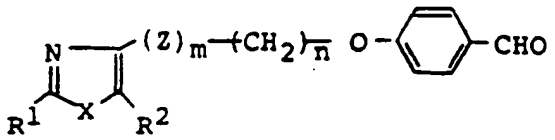
[wherein each of the symbols are as defined hereinbefore] or its salt, and

7. A process for producing a compound of the general formula:



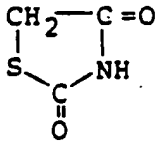
(I-5)

[wherein each of the symbols is as defined hereinbefore] or its salt, which comprises reacting a compound of the general formula:



(V)

[wherein each of the symbols is as defined hereinbefore] with a compound of the formula:



(VI)

or its salt.

8. A process for producing a compound of the general formula (I-4) or its salt, which comprises reducing a compound of the general formula (I-5) or its salt.

In the above general formulae (I), (I-1), (I-2), (I-3), (I-4), (I-5), (II), (III), (IV) and (V), the hydrocarbon residue represented by R^1 is that having 1 to 13 carbon atoms and means aliphatic hydrocarbon residues, alicyclic hydrocarbon residues, alicyclic-aliphatic hydrocarbon residues, aromatic-aliphatic hydrocarbon residues and aromatic hydrocarbon residues. The said aliphatic hydrocarbon residue is that having 1 to 8 carbon atoms and includes saturated aliphatic hydrocarbon residues of 1 to 8 carbon atoms, such as methyl ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, t-pentyl, hexyl, isohexyl, heptyl and octyl, and unsaturated aliphatic hydrocarbon residues of 2 to 8 carbon atoms, such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl; the said alicyclic hydrocarbon residue is that having 1 to 8 carbon atoms and includes saturated alicyclic hydrocarbon residues of 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and unsaturated alicyclic hydrocarbon residues of 5 to 7 carbon atoms, such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl and 2,4-cycloheptadienyl; the alicyclic-aliphatic hydrocarbon residue is those consisting of the above-described alicyclic hydrocarbon residues bonded to the above-mentioned aliphatic hydrocarbon residues but having 4 to 9 carbon atoms, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethy, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl; and the aromatic-aliphatic hydrocarbon residue is that having 7 to 13 carbon atoms and includes phenylalkyls of 7 to 9 carbon atoms, such as benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl, and naphthylalkyls of 11 to 13 carbon atoms, such as α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl, while the aromatic hydrocarbon residue for example, phenyl and naphthyls (α-naphthyl and β-naphthyl). The heterocyclic residue represented by R^1 denotes five-membered or six-membered rings containing, other than carbon, 1 to 3 atoms selected from N, O and S as a ring-forming atom and capable of bonding through carbon, and their specific examples include heteroaromatic ring groups, such as thienyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl) and oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), and saturated heterocyclic groups, such as piperidinyl (2-piperidinyl, 3-piperidinyl, 4-piperidinyl), pyrrolidinyl (2-pyrrolidinyl, 3-pyrrolidinyl), morpholinyl (2-morpholinyl, 3-morpholinyl) and tetrahydrofuryl (2-tetrahydrofuryl, 3-tetrahydrofuryl).

The hydrocarbon residue and heterocyclic residue represented by R^1 may have a substituent or substituents in their arbitrary positions. In cases in which R^1 comprehends a alicyclic group or R^1 is a saturated heterocyclic group, such groups may have 1 to 3 of lower alkyl groups (e.g., methyl, ethyl, propyl, isopropyl) of 1 to 3 carbon atoms on their rings (inclusive of the N atom). In cases in which R^1 includes a aromatic hydrocarbon group or R^1 is a hetero-aromatic ring group, such groups may have 1 to 4 of the same or different substituents on their rings (exclusive of the hetero atoms), whereby the said substituents are selected from, halogens (e.g., fluorine, chlorine, iodine), hydroxyl, cyano, trifluoromethyl, lower alkoxies (having 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy and butoxy), lower alkyls (having 1 to 4 carbon atoms, such as methyl, ethyl, pr pyl, isopropyl and butyl), lower alk xycarbonyls (having 2 to 4 carbon atoms such as methoxycarb nyl, ethoxycarb nyl, propoxycarbonyl, etc.) and l wer alkylthios (having 1 t 3 carbon atoms, such as methylthio, ethylthi , pr pylthio and isopropylthio).

The lower alkyl group represent d by R^2 has 1 to 5 carbon atoms, such as methyl, ethyl, propyl, is propyl, butyl, is butyl, sec-butyl, t-butyl and pentyl, whereupon thos having 1 to 4 carbon atoms are preferred and those having 1 to 3 carb n atoms are the most preferable. Thes alkyl groups may have a

hydroxyl group or hydroxyl gr ups in their arbitrary p sitions, with the α position being particularly preferable.

In the g neral formulae (I), (I-1), (I-2), (I-3) and (III), when L and M combine with each other and cooperate jointly to form a linkage, this is underst od to mean that the carbon atoms at both ends of this linkage combine with each other through the double bond. In cases in which L and M combine with each other and cooperate jointly to form a linkage, the compound of the general formula (I), for example, is represented by the general formula (I-5). In cases in which L and M represent independently a hydrogen atom, the compound of the general formula (I) is represented by the general formula (I-4).

The halogen represented by Y in the general formula (II) includes chlorine, bromine and iodine.

The compound of the general formula (I), which has acid nitrogen on its thiazolidine ring, forms salts with bases. Such base salts include pharmaceutically acceptable salts, such as sodium salt, potassium salt, aluminum salt, magnesium salt and calcium salt.

The compound of the general formula (I) or its salts can be produced by the following procedure.

The compound of the general formula (I) wherein *n* is 1 or its salts, namely the compound represented by the general formula (I-1) or its salts [hereinafter referred to collectively as "Compound (I-1)"] can be formed by reacting a compound of the general formula (II) with a compound of the general formula (III) or its salt [hereinafter referred to collectively as "Compound (III)"], followed by reduction of the reaction product, if desired.

The reaction of Compound (II) with Compound (III) is normally carried out in the presence of suitable solvent and base, and this reaction can afford the compound (I') namely the desired compound (I) with m = 0 and n = 1.

Examples of such a solvent include dimethylformamide, dimethylsulfoxide, tetrahydrofuran, dimethoxyethane, etc., while examples of the said base includes sodium hydride, potassium hydride, sodium amide, sodium alkoxides (e.g., sodium methoxide, sodium ethoxide), potassium alkoxides (e.g., potassium butoxide). This reaction is preferably carried out by firstly reacting 1 mole of Compound (II) with 2 moles of a base to form a dianion and subsequently adding 1 mole of Compound (II) to allow the reaction to proceed. This condensation reaction is conducted normally at 0°C to 120°C, preferably at 20°C to 100°C, and the reaction time is normally 0.5 to 5 hours.

In this reaction, the use of the compound of the general formula (II) wherein m = 1 as a starting compound can produce Compound (I-1) wherein m is 1 and Z is carbonyl. This compound, when being subjected to reduction, if desired, can be derived into Compound (I-1) wherein *m* is 1 and Z is

The compound of the general formula (I-2) or its salts [hereinafter referred to collectively as "Compound (I-2)"] can be derived through reduction into the compound of the general formula (I-3) or its salts [hereinafter referred to collectively as "Compound (I-3)"]. This reduction reaction can be allowed to proceed readily by utilizing sodium borohydride in a solvent such as an alkanol (e.g. methanol, ethanol, 2-propanol, 2-methoxyethanol), if desired, admixed with N,N-dimethylformamide. The amount of sodium borohydride to be used is 0.3 to 2 moles per mole of Compound (I-2). The reaction temperature is −10°C to 100°C, while the reaction time is 0.5 to 5 hours.

Compound (I-3) can be derived through oxidation into Compound (I-2). This oxidation reaction can be allowed to proceed readily by means of activated DMSO oxidation utilizing dimethylsulfoxide (DMSO) and an electrophilic reagent (e.g., acetic anhydride, dicyclohexylcarbodiimide (DCC), phosphorus pentaoxide, etc.), by chromic acid oxidation.

The activated DMSO oxidation can be allowed to proceed by adding an electrophilic reagent, such as acetic anhydride, DCC and phosphorus pentoxide, in DMSO, if desired, admixed with benzene, pyridine, ether, etc. The amount of DMSO to be used is normally in large excess, and the reaction temperature ranges from −10°C to 60°C, preferably from 0 to 30°C, varying depending upon the type of the electrophilic reagent to be used, while the reaction time is 1 to 30 hours. The chromic acid oxidation can be allowed to proceed by means of the methods of utilizing a Jones reagent (chromium trioxide-sulfuric acid-acetone) in chromium trioxide in acetic acid, chromium trioxide in pyridine or a previously prepared chromium trioxide-pyridine complex in dichloromethane used as a solvent. The amount of chromium (VI) to be used is normally 0.5 to 2 equivalents against Compound (I-3). The reaction temperature is −10°C to 60°C, preferably 0 to 30°C, while the reaction time is 0.5 to 50 hours.

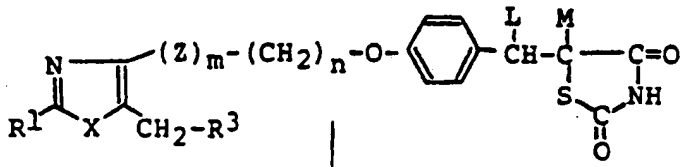
The compound of the general formula (I) wherein L and M both are independently a hydrogen atom or its salts, nam ly the compound f the general formula (I-4) or its salts (hereinaft r referred t collectively as "Compound (I-4)"), can b produced by hydrolyzing a compound of the general f rmula (IV) r its salts (hereinafter referred to collectively as "Compound (IV)"). This hydrolysis reaction is carried out normally in a suitable solvent in the presence of water and mineral acid. As th s lv nt, there are menti ned normally alkanols (e.g., methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, 2-methoxyethan l, etc.), dimethylsulfoxide, sulfolane, dioxane, dimethoxyethane, etc. The mineral acid includes, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, etc., and their amount to be used is 0.1 to 10 moles per

mole of the compound (IV), preferably 0.2 to 3 moles. The amount of water to be added is normally in large excess per mole of the compound (IV). This reaction is normally conducted under warming or heating, and the reaction temperature is ordinarily 60 to 150°C. The reaction time is normally several hours to ten-odd hours.

The compound of the general formula (I-5) or its salts [hereinafter referred to collectively as "Compound (I-5)"] can be produced by reacting a compound of general formula (V) with a compound of the formula (VI) or its salt [hereinafter referred to collectively as "Compound (VI)"]. This reaction is carried out normally in a solvent in the presence of a suitable base. As such a solvent-base system, there are used systems being suitably selected from solvents, such as alkanols (e.g., methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, 2-methoxyethanol, etc.), dimethylformamide, dimethylsulfoxide, sulfolane, acetonitrile, dioxane, dimethoxyethane and acetic acid, and bases, such as amines (e.g., pyrrolidine, piperidine, morpholine, piperazine, diethylamine, diisopropylamine, triethylamine etc.), sodium alkoxides (e.g., sodium methoxide, sodium ethoxide), potassium carbonate, sodium carbonate, sodium hydride, sodium acetate and potassium acetate. Compound (VI) is used normally at a rate of 1 to 5 mole per mole of the compound of the general formula (V), preferably 1.5 to 3.0 moles. The amount of the base to be used is 0.01 to 3.0 moles per mole of the compound (VI), preferably 0.1 to 1.0 mole. This condensation reaction is carried out normally at 0°C to 150°C, preferably 20°C to 100°C, while the reaction time is normally 0.5 to 50 hours.

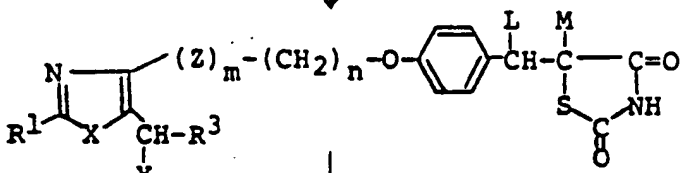
Compound (I-4) can be produced by reducing Compound (I-5). This reaction is carried out normally by catalytic hydrogenation in a solvent in the presence of a suitable catalyst. As the solvent, there are mentioned normally alkanols (e.g. methanol, ethanol, propanol, etc.), ethers (e.g. dioxane, dimethoxyethane, tetrahydrofuran, etc.), ethyl acetate, acetic acid, dimethylformamide, etc. The catalyst includes, for example, paladium black, paladium-carbon, platinum oxide, etc. This reaction can proceed at an ordinary temperature and pressure, but may be carried out at an elevated temperature (about 40 to 100°C) and pressure in order to accelerate the reaction.

The compound of the general formula (I) wherein R^2 is an alkyl group having a hydroxyl group in the α-position or its salts can also be produced for example by the procedure to be described in the following:



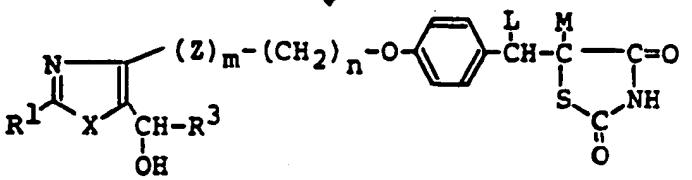
(I-6)

Halogenation



(VII)

Hydrolysis



(I-7)

[wherein R^3 is hydrogen or a lower alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, etc.); each of the other symbols is as defined hereinbefore].

Namely, the compound (I-6), that is the compound (I) wherein R^2 is lower alkyl represented by $CH_2—R^3$, or its salts [hereinafter referred to collectively as Compound (I-6)"], when halogenated, affords the compound of the general formula (VII) or its salts [hereinafter referred to collectively as "Compound (VII)"]. Compound (VII) is then converted into the objective compound (I-7) or its salts [hereinafter referred to collectively as Compound (I-7)"] by hydrolysis. The halogenation of Compound (VII) can be carried out with N-bromosuccinimide or N-chlorosuccinimide, preferably in the presence of a radical initiator, such as benzoyl peroxide and α,α'-azobisisobutyronitrile. This reaction is allowed to proceed readily by refluxing in a solvent, such as carbon tetrachloride and chloroform, and the amount of the radical initiator to be used is

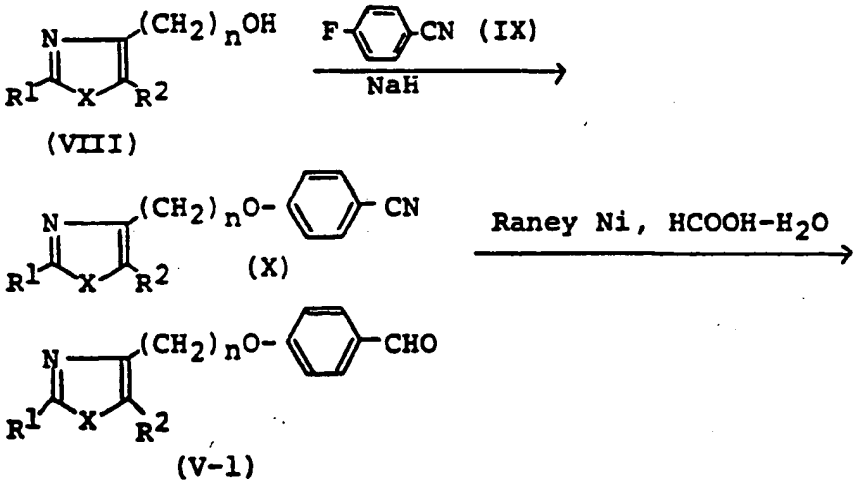
normally 0.01 to 0.2 mole per mole of Compound (I-6). The resulting α-halogenated derivative [Compound (VII)] may be hydrolyzed, after being isolated and purified, if necessary, or directly without isolation to the α-hydroxy derivative [Compound (I-7)]. This hydrolysis reaction is allowed to proceed advantageously by using a mineral acid in a suitable solvent. As the solvent, there are used dioxane, tetrahydrofuran, dimethoxyethane, etc., while as the mineral acid, there are used hydrochloric acid, sulfuric acid, etc., respectively, and the reaction temperature is 20°C to 100°C, with the reaction time ranging from 0.5 to 10 hours.

The thiazolidinedione derivative (I) and its salts as obtained in this manner can be isolated and purified by the known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase-transfer and chromatography.

The compound (I) of this invention and its salt exhibit excellent blood-glucose and blood-lipid lowering actions in mammals (e.g., mouse, rat, dog, cat, monkey, horse, and human being), and show a low degree of toxicity in terms of both acute and subacute toxicities. Therefore, the thiazolidinedione derivative (I) and its salts is of value to human being for the treatment of hyperlipemia, diabetes and their complications. With reference to the method of administration, they are normally used orally in such dosage forms as tablets, capsules, powders, granules, etc., and can also be administered parenterally in dosage forms, such as injectable solutions, suppositories and pellets, as the case may be. In the case of application as a therapeutic agent for diabetes or hyperlipemia, the compounds can be normally administered to an adult patient orally at a dose of 0.01 to 10 mg/kg a day, or parenterally at a dose of 0.005 mg to 10 mg/kg a day, whereby such doses are desirably given once a day or twice to four times a week intermittently.

The starting compound (V) of this invention can be produced, for example, by the following procedure.

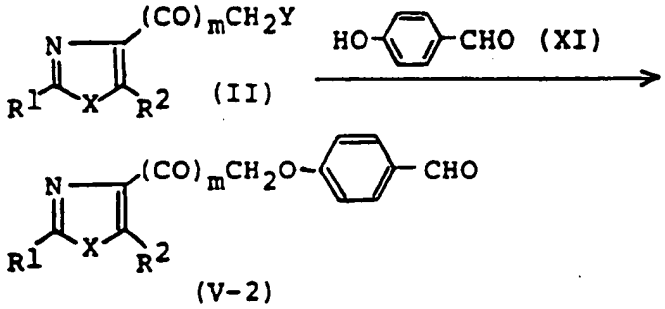
1a) Preparation of the compound (V-1), i.e. compound (V) wherein m = 0.



[wherein each of the symbols is as defined hereinbefore].

The reaction of the compound (VIII) to the compound (X) is carried out by allowing the compounds (VIII) and (IX) to undergo condensation for example in the presence of sodium hydride. This reaction can be conducted in a solvent, such as dimethylformamide, dimethylsulfoxide, tetrahydrofuran and dimethoxyethane, at −10°C to 30°C. The subsequent reaction of the compound (X) to the compound (V-1) is carried out by heating the compound with Raney nickel alloy in an aqueous formic acid solution.

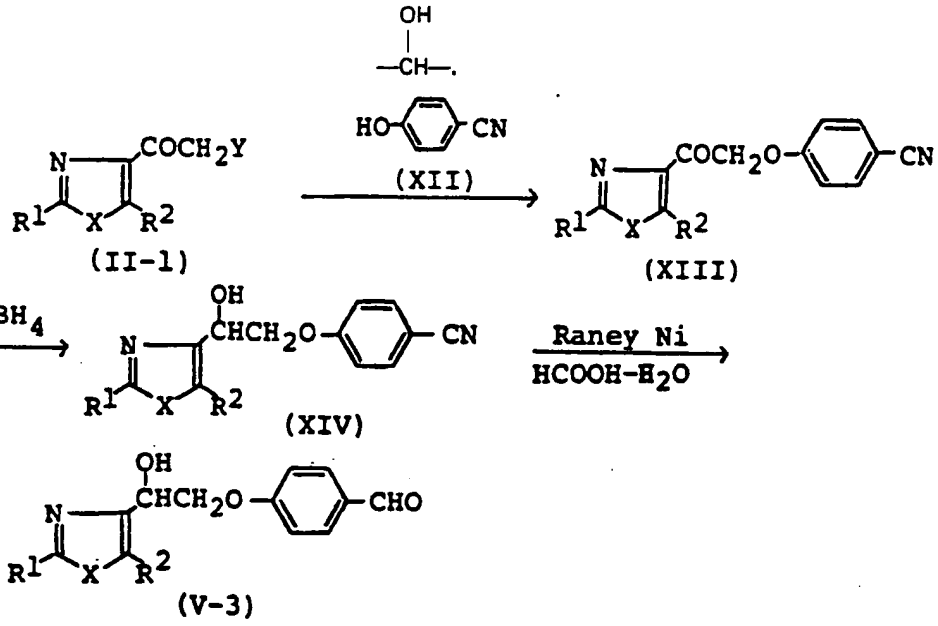
1b) Production of the compound (V-2) of the general formula (V) wherein m = 0 and n = 1, or m = n = 1 and Z = —CO—.



[wherein each of the symbols is as defined hereinbefore].

The reaction of condensation of the compound (II) with the compound (XI) to give (V-2) is normally allowed to proceed in a solvent, such as dimethylformamide, tetrahydrofuran, acetone and methyl ethyl ketone, in the presence of a base (e.g., sodium carbonate, potassium carbonate, etc.) at 0°C to 150°C.

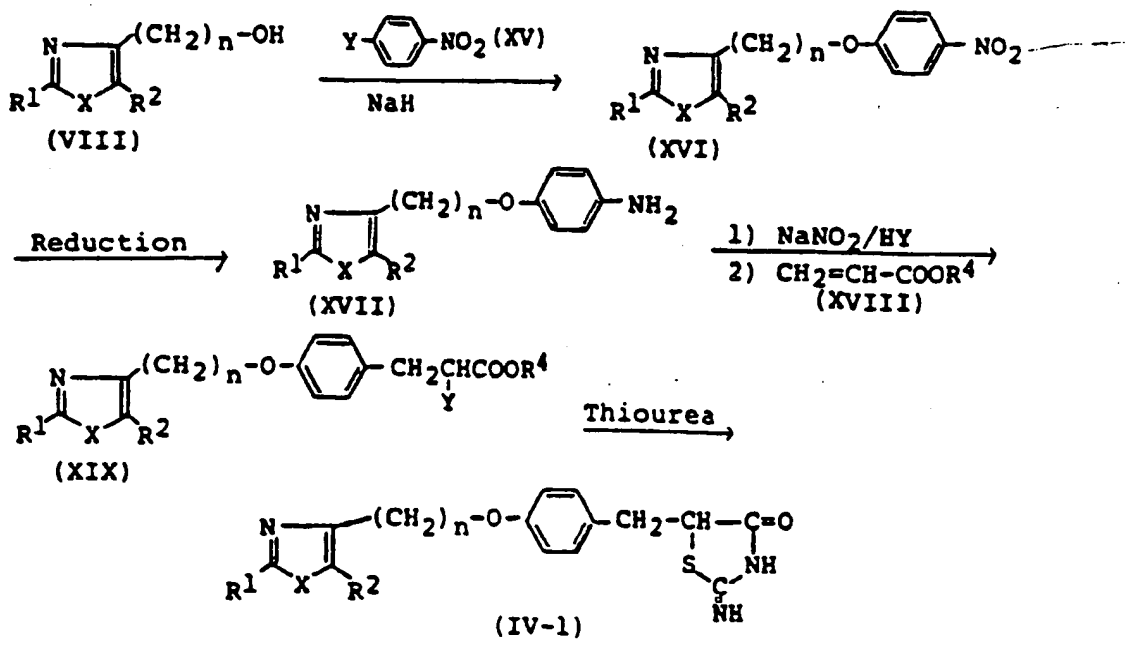
1c) Preparation of the compound (V-3), i.e. compound (V) wherein m = n = 1 and Z =



[wherein each of the symbols is as defined hereinbefore].

The reaction of the compound (II—1) with the compound (XII) can be carried out in a manner similar to the above-described reaction between the compounds (II) and (XI), and the resulting compound (XIII) is reduced in accordance with the conventional procedure by use of sodium borohydride in a solvent such as methanol, ethanol, and N,N-dimethylformamide, or their mixture to give the compound (XIV), which can subsequently be converted to (V—3) by a reaction similar to the above-described reaction of deriving (X) into (V—1).

2a) Preparation of the compound (IV—1), i.e. compound (IV) wherein m = 0.



[wherein R^4 is hydrogen or a lower alkyl group; other symbols are as defined hereinbefore].

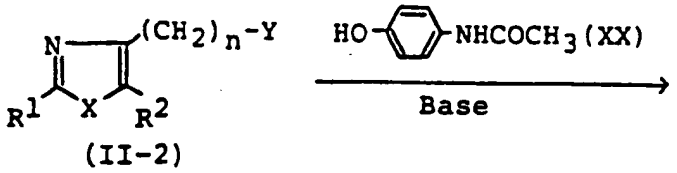
The lower alkyl group represented by R^4 in the above general formulae (XVIII) and (XIX) includes alkyl groups of 1 to 4 carbon at ms, such as methyl, ethyl, propyl and butyl.

The reaction of the compound (VIII) to the compound (XVI) is carried out by condensation of the compound (VIII) with the compound (XV) for example in the presence of sodium hydride. This reaction can be conducted in a solvent, such as dimethylformamide and tetrahydrofuran, at −10°C to 30°C. The subsequent reaction of the compound (XVI) to the compound (XVII) is readily carried out, for example, by catalytic reduction of the compound (XVI) in accordance with the conventional method by the use of palladium carbon as a catalyst or by reduction of the compound in accordance with the conventional method by the use of zinc or iron and acetic acid. The compound (XVII) may be isolated as a pure product or can be subjected to the reaction in the subsequent step without being isolated and purified. The reaction of the compound (XVII) to the compound (XIX) is carried out by means of the so-called Meerwein arylation reaction which involves diazotization of the compound (XVII) in the presence of a hydrohalogenic acid (HY), followed by reaction with acrylic acid or its ester (XVIII) in the presence of a copper catalyst (e.g., cuprous oxide, cupric oxide, cuprous chloride, cupric chloride, cuprous bromide, cupric bromide, etc.). The compound (XIX) can be purified by chromatography, and can also be subjected to the reaction in the subsequent step without being isolated and purified.

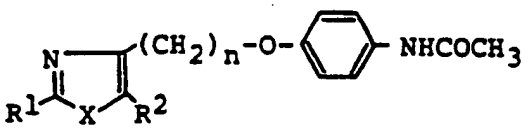
The compound (IV—1) can be produced by reacting thereafter the compound (XIX) with thiourea.

This reaction is carried out normally in a solvent, such as alcohols (e.g., methanol, ethanol, propanol, 2-propanol, butanol, isobutanol, 2-methoxyethanol, etc.), dimethylsulfoxide and sulfolane. The reaction temperature is normally 20°C to 180°C, preferably 60°C to 150°C. The amount of thiourea to be used is 1 to 2 moles per mole of the compound (XIX). This reaction proceeds with a hydrogen halide being formed as a by-product, and may be carried out in the presence of sodium acetate, potassium acetate, etc. for the purpose of capturing such a by-product. The amount of these compounds to be used is normally 1 to 1.5 moles per mole of the compound (XIX). This reaction can yield the compound (IV—1), which can be isolated, if desired, but may be subjected to the following hydrolysis step directly without being isolated.

The compound (XVII) having a hydroxy-substituted phenyl group as R^1 can be synthesized by condensation of the compound (VIII) having a benzyloxy-substituted phenyl group as R^1 with the compound (XV) and catalytic reduction of the resulting compound (XVI) to perform simultaneously reduction of the nitro group and debenzylation. Also, the compound (XVII) can be synthesized by the following procedure.



(II-2)

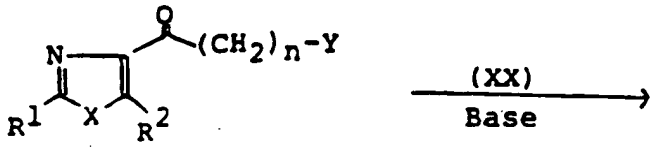


(XXI)

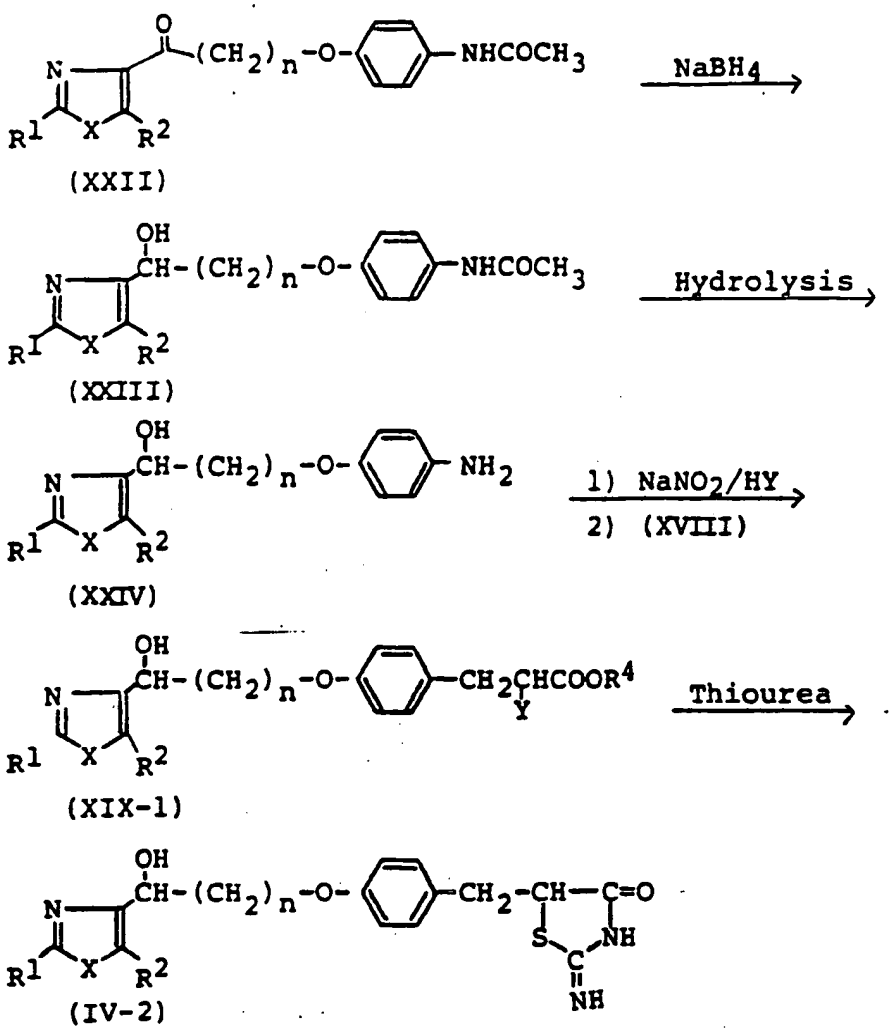
[wherein each of the symbols is as defined hereinbefore].

The condensation of the compound (II—2) with the compound (XX) to give the compound (XXI) can be normally conducted in a solvent, such as dimethylformamide, tetrahydrofuran, acetone and methyl ethyl ketone, in the presence of a base (e.g., sodium carbonate, potassium carbonate, etc.) at 0°C to 150°C. Subsequently, (XXI) is hydrolyzed to the compound (XVII). This hydrolysis reaction can be carried out with a mineral acid (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, etc.) or more preferably with an alkali hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.) in a solvent, such as methanol, ethanol, propanol, 2-propanol and 2-methoxypropanol, under reflux.

2b) Preparation of the compound (IV—2), i.e. compound (IV) wherein m = 1.



(II-3)

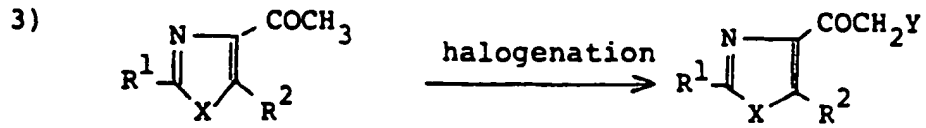


(XXII) (XXIII) (XXIV) (XIX-1) (IV-2)

[wherein each of the symbols is as defined hereinbefore].

The condensation reaction of the compound (II—3) with the compound (XX) can be carried out in a manner similar to that of the above-mentioned reaction of the compound (II—2) with the compound (XX). The resulting compound (XXII) is reduced, by the conventional method, with sodium borohydride in methanol or ethanol to give the compound (XXIII), which then can be hydrolyzed, in a manner similar to that of the above hydrolysis of (XXI), to afford the compound (XXIV). By the same procedure as that used in producing (IV—1) from (XVII), the compound (XXIV) can be converted into (IV—2) through (XIX—1).

The starting materials (II) wherein m=0, can be prepared, for example, by the methods described in J. Am. Chem. Soc., *56*, 470 (1934) and Japanese Unexamined Patent Publication No. 219169 (1983), or by a procedure analogous to them. Compounds (II—4), i.e. compound (II) wherein m=1, can be produced by the following method:



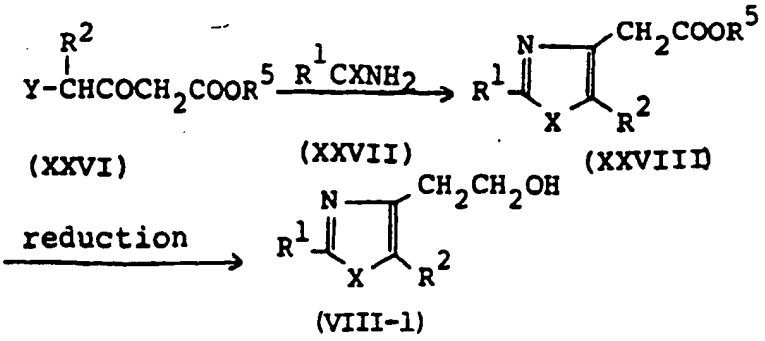
(XXV) (II-4)

[wherein each of the symbols is as defined hereinbefore]

This reaction is performed by halogenating compounds (XXV) which can be produced, for example, by the methods described in Chem. Ber., *84*, 96 (1951), Nihon Kagaku Zasshi, *86*, 942 (1965), Bull. Soc. Chim. France, *9* 3862 (1968), J. Chem. Soc., C., 1397 (1968) and German Patent 2152557, or by a procedure analogous to them. The halogenation is conducted for instance, with a halogen, preferably bromine, in a suitable solvent (e.g. chloroform, carbon tetrachloride) at 30—60°C.

The starting compounds (VIII) for the preparation of the iminothiazolidine comp unds (IV—1) are produced by the following methods.

4a) Production of (VIII—1), i.e. compound (VIII) wherein n=2.



(XXVI) (XXVII) (XXVIII)

[wherein R^5 is a lower alkyl]

The reaction of (XXVI) with (XXVII) is easily conducted in a solvent such as an alkanol (e.g. methanol, ethanol, propanol, etc.), or without using a solvent, by heating at about 40—150°C.

The resulting (XXVIII) is reduced by a conventional method, for example, using lithium aluminum hydride to yield (VIII—1). The compound (XXVIII) wherein x=0 is also prepared by the method described in Japanese Unexamined Patent Publication Nos. 201771 (1983) and 219169 (1983)/ or by a procedure analogous to them.

4b) Compound (VIII) wherein n=1 can be prepared, for example, by the method described in Japanese Unexamined Patent Publication No. 219169 (1983), or by a procedure analogous to it.

The examples, reference examples and experiment examples are described below to illustrate this invention more specifically, but it is to be understood that this invention should not be limited to these examples.

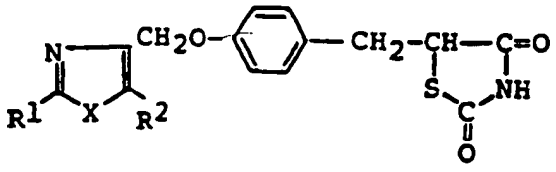
Example 1

To a solution of 5-(4-hydroxybenzyl)-2,4-thiazolidinedione (9.4 g) in N,N-dimethylformamide (80 ml) was added 60% sodium hydride in oil (3.4 g), and the mixture was stirred for 30 minutes. Then, a solution of 4-chloromethyl-2-phenyl oxazole (9.6 g) in N,N-dimethylformamide (20 ml) was added dropwise thereto at room temperature. After being stirred at 70°C for 1 hour, the reaction solution was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated to give 5-[4-(2-phenyl-4-oxazolylmethoxy)benzyl)-2,4-thiazolidinedione (9.1 g, 47.4%). Recrystallization from ethanol yielded colorless needles. m.p. 188—189°C. Elemental analysis for $C_{20}H_{16}N_2O_4S$; Calcd.: C, 63.15; H, 4.24; N, 7.36. Found: C, 63.19; H, 4.16; N, 7.23.

Examples 2 to 9

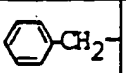
By a procedure similar to that of Example 1, there were obtained the compounds shown in Table 1.

Table 1:



Example No.	R^1	R^2	X	Melting point, °C	Recrystallizing solvent	Yield %
2		H	S	164-165	Acetone-hexane	40.5
3	C_3H_7-	H	O	114-115	Ethanol	35.8
4	CH_3	H	S	181-182	Methanol-dichloro-methane	39.7
5	CH_3	H	O	192-193	Methanol-dichloro-methane	28.3

TABLE 1 (continued)

Example No.	R^1	R^2	X	Melting point, °C	Recrystallizing solvent	Yield %
6		CH_3	O	162-163	Ethyl acetate-hexane	79.0
7		H	S	205-206	Methanol	12.6
8		H	S	209-211	Methanol	39.8
9		CH_3	O	258-260	Methanol	28.9

Example 10

60% sodium hydride in oil (1.32 g) was added to solution of 5-(4-hydroxybenzyl)-2,4-thiazolidinedione (3.35 g) in N,N-dimethylformamide (30 ml), and the mixture was stirred for 30 minutes. Then, solution of 4-chloromethyl-2-(1-methylcyclohexyl)oxazole (3.85 g) in N,N-dimethylformamide (5 ml) was added dropwise thereto at room temperature. After being stirred at 60°C for 1 hour, the reaction solution was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The oily residue was chromatographed on a column of silica gel (70 g). Elution with hexane-ethyl acetate (2:1, V/V) gave 5-{4-[2-(1-methylcyclohexyl)-4-oxazolylmethoxy]benzyl}-2,4-thiazolidinedione as an oily substance. A solution of sodium 2-ethylhexanoate in isopropanol (2N, 3 ml) was added to the oily substance, and treated with ether. The crystals which separated out were collected by filtration to give 5-{4-[2-(1-methylcyclohexyl)-4-oxazolylmethoxy]benzyl}-2,4-thiazolidinedione·sodium salt (2.3 g, 36.3%). Recrystallization from methanol afforded colorless plates. m.p. 285—287°C (decomp.)

Elemental analysis for $C_{21}H_{23}N_2O_4SNa$, Calcd.: C, 59.70; H, 5.49; N, 6.63. Found: C, 59.76; H, 5.56; N, 6.82.

Example 11

By a procedure similar to that of Example 10, there was obtained 5-[4-(1-cyclohexyl-4-thiazolylmethoxy)benzyl]-2,4-thiazolidinedione sodium salt. Yield 20.4%. Recrystallization from methanol afforded colorless prisms. m.p. 298—300°C (decomp.) Elemental Analysis for $C_{20}H_{21}N_2O_3S_2Na$, Calcd.: c, 56.59; H, 4.99; N, 6.60. Found: C, 56.42; H, 5.02; N, 6.72.

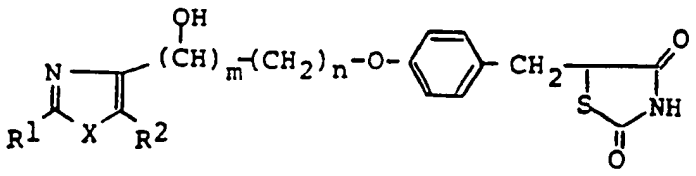
Example 12

A mixture of 2-imino-5-{4-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-4-thiazolidinone (18.8 g), 2N—HCl (200 ml) and ethanol (200 ml) was heated under reflux for 12 hours. The solvent was distilled off under reduced pressure. The residue was neutralized with saturated aqueous solution of sodium hydrogen carbonate, and extracted with chloroform. The chloroform layer was washed with water and dried ($MgSO_4$). The solvent was distilled off, whereby 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-thiazolidinedione (18.0 g, 95.7%) was obtained. Recrystallization from ethanol afforded colorless needles. m.p. 113—114°C. Elemental Analysis for $C_{22}H_{20}N_2O_4S$, Calcd.: C, 64.69; H, 4.93; N, 6.86. Found: C, 64.48; H, 4.91; N, 6.75.

Examples 13 to 32

By a procedure similar to that of Example 12, there were obtained the compounds shown in Table 2.

Table 2:



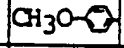
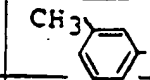
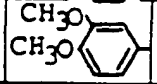
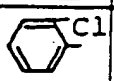
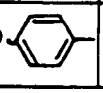
Example No.	m	n	R^1	R^2	X	Melting point, °C	Recrystallizing solvent	Yield %
13	0	1		H	O	188-189	Ethanol	55.6
14	0	2	CH_3	H	S	142-143	methanol	75.2
15	0	2	CH_3	H	O	184-185	Methanol-dichloro-methane	46.2
16	0	2		H	S	113-114	Methanol	90.8
17	0	2		H	O	109-110	Ethyl acetate-hexane	67.9
18	0	2	CH_3	CH_3	O	200-201	Methanol-chloroform	91.2
19	0	2	C_3H_7	H	O	87-88	Ether-hexane	27.9
20	0	2	C_2H_5	H	S	148-149	Ethanol-dichloro-methane	84.3
21	0	2	i-C_3H_7	H	S	107-108	Ethyl acetate-hexane	72.6
22	1	1		CH_3	O	165-166	Acetone-hexane	51.5
23	0	2		C_2H_5	O	109-111	Ethyl acetate-hexane	88.7
24	0	2		CH_3	O	167-168	Ethanol	93.5
25	0	2	CH_3	C_2H_5	O	189-190	Ethanol-chloroform	90.1
26	0	2		CH_3	O	114-115	Methanol	52.1
27	0	2		CH_3	O	144-145	Methanol-dichloromethane	60.0
28	1	1	CH_3	CH_3	O	214-215	Ethanol-chloroform	33.6

TABLE 2 (continued)

Example No.	m	n	R^1	R^2	X	Melting point, °C	Recrystallizing solvent	Yield %
29	0	2		CH_3	O	90-100	Ethyl acetate-hexane	83.1
30	0	2		CH_3	O	167-168	Ethanol-dichloromethane	89.1
31	0	2		CH_3	O	93-94	Ether-hexane	67.6
32	0	2		CH_3	O	213-214	Methanol-chloroform	67.3

Example 33

A mixture of 2-imino-5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyl]-4-thiazolidinone (11.4 g), 1N·H_2SO_4 (100 ml) and dioxane (100 ml) was stirred at 80°C for 5 hours, and poured in water. The aqueous mixture was extracted with chloroform. The chloroform layer was washed with water, dried ($MgSO_4$) and concentrated. The oily residue was chromatographed on a column of silica gel (200 g), and from the fractions eluted with chloroform-methanol (100:1, V/V), there was obtained 5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyl]-2,4-thiazolidinedione (6.7 g, 58.8%). Recrystallization from ethyl acetate-hexane afforded colorless plates. m.p. 162—163°C. Elemental analysis for $C_{21}H_{18}N_2O_4S$, Calcd.: C, 63.95; H, 4.60; N, 7.10. Found: C, 63.84; H, 4.63; N, 6.90.

This product showed the IR and NMR spectra in accordance with those of the compound obtained in Example 6.

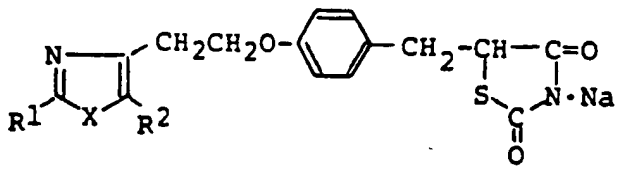
Example 34

A mixture of 2-imino-5-<4-{2-[5-methyl-2-(1-methylcyclohexyl)-4-oxazolyl]ethoxy}benzyl>-4-thiazolodinone (9.5 g), 2N HCl (100 ml) and ethanol (100 ml) was heated under reflux for 15 hours. The reaction solution was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The oily residue was dissolved in methanol (10 ml), and 10 g of 28% solution of sodium methylate in methanol was added to the solution. Ether (100 ml) was added to the solution, and the crystals which separated out were collected by filtration and recrystallization from ethanol gave 5<4-{2-[5-methyl-2-(1-methylcyclohexyl)-4-oxazolyl]-ethoxy}benzyl>-2,4-thiazolidinedione·sodium salt (5.1 g, 51.5%). Colorless prisms, m.p. 250—251°C (decomp.). Elemental analysis for $C_{23}H_{27}N_2O_4SNa$, Calcd.: C, 61.32; H, 6.04; N, 6.22. Found: C, 61.47; H, 6.15; N, 6.48.

Examples 35 to 37

By a procedure similar to that of Example 34, there were obtained the compounds shown in Table 3.

Table 3:



Example No.	R^1	R^2	X	Melting point °C (decomp.)	Recrystallizing solvent	Yield %
35		H	S	289-291	Methanol	81.0
36		H	O	269-271 (1/2 hydrate)	Ethanol	33.6
37		CH_3	O	273-275	Methanol-ethanol	71.2

Example 38

1) N-Bromosuccinimide (2.75 g) was added portionwise to a solution of 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-thiazolidindione (6.0 g) and α,α'-azobisisobutyronitrile (0.5 g) in carbon tetrachloride (150 ml) under reflux. After refluxing for another 10 minutes, the reaction mixture was washed with water and dried ($MgSO_4$). The solvent was distilled off to give 5-{4-[2-(5-bromomethyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-thiazolidinedione as a crude oily substance (about 8 g). IR (neat) cm^{-1}: 1750, 1690. NMRδ (ppm) in $CDCl_3$: 3.03 (2Ht J=7Hz), 2.9 to 3.2 (1H, m), 3.48 (1H, d.d, J=14 and 5Hz), 4.24 (2H, t, J=7Hz), 4.45 (1h, d.d, J=9 and 5Hz), 4.61 (2H, s), 6.81 (2H, d, J=9Hz), 7.10 (2H, d, J=9Hz), 7.4 (3H, m), 8.0 (2H, m), 8.70 (1H, broad s).

2) The oily substance (about 8 g) obtained in 1) was dissolved in dioxane (100 ml), and 2N·HCl (100 ml) was added to the solution. The mixture was refluxed for 7 hours and poured into water. The aqueous mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated, and the residue was chromatographed on a column of silica gel (200 g). From the fractions eluted with ether-hexane (1:1, V/V), there was obtained 5-{4-[2-(5-hydroxymethyl-2-phenyl-4-oxazolyl)ethoxy]-benzyl}-2,4-thiazolidinedione (1.31 g, 21.0%). Recrystallization from acetone-hexane yielded colorless scales. m.p. 98—99°C. Elemental analysis for $C_{22}H_{20}N_2O_5S$, Calcd.: C, 62.25; H, 4.75; N, 6.60. Found: C, 62.08; H, 4.56; N, 6.49.

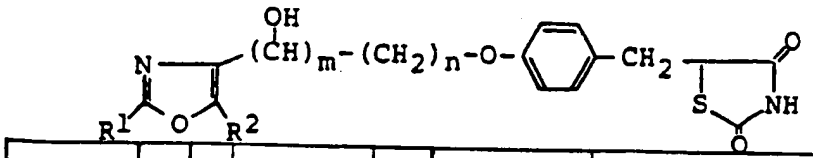
Example 39

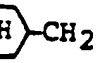
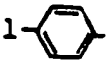
By a procedure similar to that of Example 1, there was obtained 5-[4-(4-thiazolylmethoxy)benzyl]-2,4-thiazolidinedione. Yield of 18.1%. Recrystallization from acetone-hexane afforded colorless needles, m.p. 151—153°C. Elemental analysis for $C_{14}H_{12}N_2O_3S_2$, Calcd.: C, 52.42; H, 3.78; N, 8.74. Found: C, 52.75; H, 3.78; N, 8.74.

Examples 40 to 45

By a procedure similar to that of Example 12, there were obtained the compounds shown in Table 4.

Table 4.



Example No.	m	n	R^1	R^2	Melting point, °C	Recrystallizing solvent	Yield %
40	0	2		CH_3	135-136	Acetone-hexane	89.4
41	0	2		CH_3	173-174	Ethanol	92.1
42	0	2		CH_3	161-162	Ethanol	95.0
43	0	2		CH_3	163-164	Ethanol	88.0
44	1	1		CH_3	Oily material	-	55.0
45	0	3		CH_3	130-131	Ethyl acetate-hexane	94.0

Example 46

By a procedure similar to that of Example 34, there was obtained 5-<4-{2-[5-methyl-2-(1-methyl-3-cyclohexenyl)-4-oxazolyl]ethoxy}benzyl>-2,4-thiazolidinedione·sodium salt. Yield 79.2%. Recrystallization from methanol-ethyl acetate afforded colorless prisms. m.p. 245—246°C (decomp.). Elemental analysis for $C_{23}H_{25}N_2O_4SNa$, Calcd.: C, 61.59; H, 5.62; N, 6.25. Found: C, 61.70; H, 5.59; N, 6.01.

Example 47

Acetic anhydride (1.0 ml) was added to a solution of 5-{4-[2-(2,5-dimethyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-2,4-thiazolidinedione (0.5 g) in dimethylsulfoxide (10 ml), and the mixture was

allowed to stand overnight and poured into water. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The oily residue was chromatographed on a column of silica gel (40 g), and from the fractions eluted with benzene-acetone (9:1, V/V), there was obtained 5-{4-[2-(2,5-dimethyl-4-oxazolyl)-2-oxoethoxy]benzyl}-2,4-thiazolidinedione (0.24 g, 48.3%). Recrystallization from ethyl acetate-hexane afforded colorless plates, m.p. 161—162°C. Elemental analysis for $C_{17}H_{18}N_2O_5S$, Calcd.: C, 56.66; H, 4.47; N, 7.77. Found: C, 56.62; H, 4.38; N, 7.60.

Example 48

By a procedure similar to that of Example 47, there was obtained 5-{4-[2-(5-methyl-3-phenyl-4-oxazolyl)-2-oxoethoxy]benzyl}-2,4-thiazolidinedione. Yield 81.3%. Recrystallization from ethyl acetate-hexane afforded colorless prisms, m.p. 168—169°C.

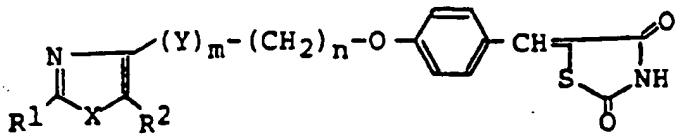
Example 49

A mixture of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]benzaldehyde (5.0 g), 2,4-thiazolidinedione (3.8 g), piperidine (0.32 ml) and ethanol (100 ml) was stirred under reflux for 5 hours. After cooling, the crystals which separated out were collected by filtration to give 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-thiazolidinedione (5.1 g, 76.8%). Recrystallization from chloroform-ethanol afforded colorless needles, m.p. 213—214°C. Elemental analysis for $C_{22}H_{18}N_2O_4S$, Calcd.: C, 65.01; H, 4.46; N, 6.89. Found: C, 64.81; H, 4.55; N, 6.78.

Examples 50 to 63

By following a procedure similar to that of Example 48, there were obtained the compounds as shown in Table 5.

Table 5:



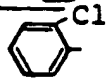
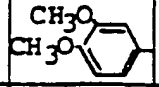
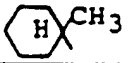
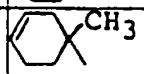
Example No.	R^1	R^2	X	m	Y	n	Melting point, °C	Recrystallizing solvent	Yield %
50	CH_3	H	S	0	-	2	215-216	Ethanol-chloroform	81.6
51		H	S	0	-	1	235-237	Methanol-chloroform	89.9
52		H	S	0	-	2	210-211	Methanol-chloroform	90.6
53		H	O	0	-	1	244-246	DMF-water	80.5
54		C_2H_5	O	0	-	2	175-176	Ethanol-chloroform	71.9
55		CH_3	O	0	-	2	217-218	Ethanol-chloroform	82.7
56		CH_3	O	0	-	2	214-215	Ethanol-dichloromethane	91.2
57		CH_3	O	0	-	2	185-187	Ethanol-chloroform	67.0

TABLE 5 (continued)

Example No.	R^1	R^2	X	m	Y	n	Melting point, °C	Recrystallizing solvent	Yield %
58		CH_3	O	0	-	2	243-244	DMF-water	83.1
59		CH_3	O	0	-	2	221-222	Ethanol-chloroform	48.2
60	CH_3	CH_3	O	1	-CO-	1	234-235	Ethanol-chloroform	62.7
61		CH_3	O	1	-CH(OH)-	1	252-253.5	Methanol-chloroform	58.6
62		CH_3	O	0	-	2	172-175	Ethanol-chloroform	53.1
63		CH_3	O	0	-	2	158-159	Ethanol-chloroform	56.0

Example 64

60% sodium hydride in oil (0.24 g) was added to a solution of 5-(4-hydroxybenzylidene)-2,4-thiazolidinedione (0.664 g) in N,N-dimethylformamide (20 ml), and the mixture was stirred for 30 minutes. A solution of 4-chloromethyl-5-methyl-2-phenyloxazole (0.623 g) in N,N-dimethylformamide (10 ml) was added dropwise to the mixture under ice-cooling. After stirring at room temperature for 5 hours, the reaction solution was poured into water. The aqueous mixture was made acid with acetic acid and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on a column of silica gel (50 g). From the fractions eluted with ethyl acetatehexane (1:2, V/V), there was obtained 5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)-benzylidene]-2,4-thiazolidinedione (0.49 g, 40.8%). Recrystallization from chloroform-methanol afforded colorless prisms, m.p. 225—226°C. Elemental analysis for $C_{21}H_{16}N_2O_4S$, Calcd.: C, 64.27; H, 4.11; N, 7.14. Found: C, 64.49; H, 3.96; N, 6.86.

Example 65

60% sodium hydride in oil (0.24 g) was added to a solution of 5-(4-hydroxybenzylidene)-2,4-thiazolidinedione (0.663 g) in N,N-dimethylformamide (20 ml) and the mixture was stirred for 30 minutes. Then, a solution of 4-bromoacetyl-5-methyl-2-phenyloxazole (0.841 g) in N,N-dimethylformamide (10 ml) was added dropwise to the mixture under ice-cooling. After stirring under ice-cooling for 30 minutes, the reaction solution was poured into ice-cold water. The aqueous mixture was made acid with acetic acid. The solid which precipitated was collected by filtration, washed with water, and crystallized from acetone to give 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzylidene}-2,4-thiazolidinedione (0.42 g, 32.3%). Recrystallization from chloroform-ethanol yielded colorless needles, m.p. 244—245°C. Elemental analsysis for $C_{22}H_{16}N_2O_5S$, Calcd.: C, 62.85; H, 3.84; N, 6.66. Found: C, 62.80, H, 3.69; N, 6.93.

Example 66

Sodium borohydride (0.16 g) was added to a suspension of 5-{4-[2-(2,5-dimethyl-oxazolyl)-2-oxoethoxy]benzylidene}-2,4-thiazolidinedione (1.5 g) in methanol-N,N-dimethylformamide (1:1, V.V, 40 ml) under ice-cooling. After stirring under ice-cooling for 20 minutes, the reaction solution was poured into ice-water, and the aqueous mixture was made acid with acetic acid, and the crytals which separated out were collected by filtration to give 5-{4-[2-(2,5-dimethyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-2,4-thiazolidinedione (1.47 g, 97.5%). Recrystallization from chloroform-ethanol afforded colorless prisms, m.p. 223—224°C. Elemental analysis for $C_{17}H_{16}N_2O_5S$, Calcd.: C, 56.66; H, 4.47; N, 7.77. Found: C, 56.36; h, 4.55; N, 7.56.

Example 67

By a procedure similar to that of Example 66, there was obtained 5-{4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-thiazolidinedione (the same compound as that obtained in Example 61 from 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]b nzylidene}-2,4-thiazolidinedione. M.p. 252—253°C. Yield 98.4%.

Example 68

0.32 ml f 28% sodium methylate in methanol was added dropwise t a suspension of 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-thiazolidinedione (0.50 g) in methanol (10 ml). The reacti n s lution was conc ntrated, and diluted with ethyl eth r. The crystals which separated out were

collected by filtration to give sodium salt (0.43 g, 81.6%) of 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-benzylidene}-2,4-thiazolidinedione. Recrystallization from methan l afforded colorless prisms, m.p. 286—288°C (d c mp.). Elemental analysis for $C_{22}H_{17}N_2 \cdot O_4SNa$, Calcd.: C, 61.68; H, 4.00; N, 6.54. Found: C, 61.44; H, 3.82; N, 6.85.

Example 69

A stirred mixture of 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-thiazolidinedione (500 mg), 10% Pd-C (50% wet, 1.0 g) and acetic acid (50 ml) was hydrogenated at 70°C and at atmospheric pressure for 3 hours. Methanol (20 ml) and chloroform (20 ml) were added to the mixture and the whole was heated at 60°C for 5 minutes. The mixture was filtered hot and the filtrate was concentrated in vacuo. A solution of the residue in ethyl acetate was successively washed with saturated aqueous sodium bicarbonate solution and water, and dried over magnesium sulfate. The solvent was removed and the residue recrystallized from ethanol to yield 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-thiazolidinedione (the same compound as that obtained in Example 12) as crystals (415 mg, 82.7%). m.p. 113—114°C.

Example 70

A stirred mixture of 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzylidene}-2,4-thiazolidinedione (1.0 g), Pd-black (3 g) and dioxane (100 ml) was hydrogenated at 40°C and at atmospheric pressure. After 4 hours, another Pd-black (3 g) was added and hydrogenation was continued for 4 hours. The catalyst was filtered off and the filtrate was concentrated to yield 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzyl}-2,4-thiazolidinedione (the same compound as that obtained in Example 48) as crystals (0.95 g, 94.1%). Recrystallization from ethyl acetate-hexane gave colorless needles, m.p. 168—169°C.

Reference Example 1

A mixture of butyramide (19.88 g) and 1.3-dichloroacetone (24.14 g) was heated at 130°C for 1.5 hours. After cooling, the mixture was diluted with water, neutralized with aqueous sodium bicarbonate solution and extracted with ethyl ether. The extract was washed with water, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on silica gel with acetone-hexane (1:9) to yield 4-chloromethyl-2-propyloxazole as an oil (10.70 g, 35.3%). NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.5 Hz), 1.79 (2H, sext, J=7.5 Hz), 2.72 (2H, t, J=7.5 Hz), 4.47 (2H, s), 7.53 (1H, s).

Reference Example 2

A mixture of benzamide (60.0 g) and ethyl 4-chloroacetoacetate (49.4 g) was heated at 120°C for 2 hours. After cooling, aqueous sodium bicarbonate solution was added thereto and the mixture was extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on silica gel with ethyl ether-hexane (1:9) to yield ethyl 2-phenyl-4-oxazole-acetate as an oil (26.4 g, 28.0%). NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz), 3.68 (3H, s), 4.15 (2H, q, J=7 Hz), 7.4 (3 H, m), 7.67 (1H, s), 8.0 (2H, m).

Reference Example 3

A mixture of cyclohexanethiocarboxamide (5.0 g), ethyl 4-chloroacetoacetate (5.74 g), ethanol (50 ml) was heated under reflux for 1 hour. After dilution with water, mixture was extracted with ethyl acetate. The extract was washed with aqueous sodium bicarbonate solution and water, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel with ethyl acetate-hexane (1:4) to yield ethyl 2-cyclohexyl-4-thiazoleacetate as an oil (6.3 g, 70.9%). IR (Neat): 1735, 1255cm^{-1}. NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz), 1.2—2.3 (10H, m), 2.97 (1H, m), 3.77 (2H, s), 4.17 (2H, q, J=7 Hz), 7.0 (1H, s).

Reference Example 4

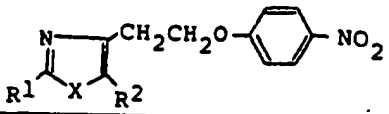
A solution of methyl 5-methyl-2-phenyl-4-oxazoleacetate (54 g) in dry ethyl ether (150 ml) was added dropwise to a stirred ice-cooled suspension of lithium aluminum hydride (8.8 g) in dry ethyl ether (700 ml) during 1.5 hours. Ethyl acetate (20 ml) was added dropwise thereto with ice-cooling and then water (50 ml) was added cautiously thereto. The resulting white precipitate was filtered off and the filtrate was concentrated to give 2-(5-methyl-2-phenyl-4-oxazolyl)ethanol as crystals (45.8 g, 96.2%). Recrystallization from ethyl acetate-hexane gave colorless rods, m.p. 73—74°C.

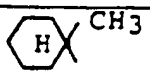
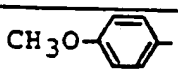
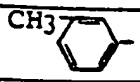
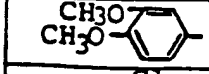
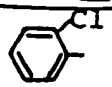
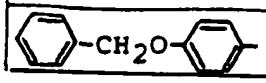
Reference Example 5

2-(2,5-Dimethyl-4-oxazolyl)ethanol (17.0 g) and 4-fluoronitrobenzene (17.0 g) were dissolved in N,N-dimethylformamide (150 ml), and 60% sodium hydride in oil (6.0 g) was added dropwise to the solution under vigorous stirring. After stirring at room temperature for 1 h ur, the reaction mixture was poured int water (1 l) and the crystals which separated ut were c llected by filtration and recrystallized from ethyl acetate-hexane to give 4-[2-(2,5-dimethyl-4-oxazolyl)ethoxy]nitr benzen (27.5 g, 87.0%). Colorless c lumns, m.p. 97—98°C. Elemental analysis for $C_{13}H_{14}N_2O_4$, Calcd.: C, 59.94; H, 5.38; N, 10.68. Found: C, 59.72; H, 5.44; N, 10.63.

By a procedure similar to the ab ve precedure, there were obtained the compounds shown in Table 6.

Table 6:



R^1	R^2	X	Melting point, °C	Recrystallizing solvent	Yield %
CH_3	H	S	101-102	Methanol-ether	70.0
CH_3	H	O	101-102	Methanol	71.3
	H	S	102-103	Methanol	50.2
	H	O	112-113	Methanol	92.2
	CH_3	O	Oily material	-	92.0
	CH_3	O	94-95	Methanol	80.1
C_3H_7	H	O	70-71	Ether-hexane	47.6
	H	S	62-63	Methanol	73.2
	H	O	61-62	Methanol	70.6
C_2H_5	H	S	63-64	Ethyl acetate-hexane	75.7
$i\text{-}C_3H_7$	H	S	62-63	Ethyl acetate-hexane	67.8
	C_2H_5	O	71-72	Ethanol	91.6
	CH_3	O	113-114	Ethyl acetate-hexane	82.1
CH_3	C_2H_5	O	89-90	Ether-hexane	77.6
	CH_3	O	Oily material	-	70.5
	CH_3	O	121-122	Methanol-dichloromethane	69.1
	CH_3	O	107-108	Methanol-water	74.7
	CH_3	O	79-80	Ethanol	85.4
	CH_3	O	124-125	Ethanol-chloroform	91.5
	CH_3	O	89-90	Ether-hexane	58.0
	CH_3	O	137-138	Methanol-dichloromethane	74.2

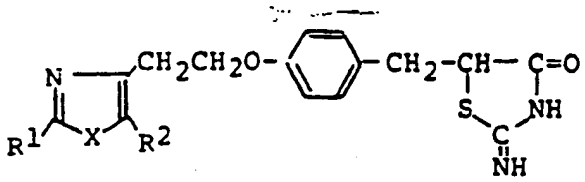
Reference Example 6

1) A solution of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]nitrobenzene (10.5 g) in methanol (100 ml) was subjected to a catalytic hydr genation over 10% Pd-C (50% wet, 3.0 g). After the catalayst was filtered off, the filtrate was concentrated to give an amino derivative as an oily substance. This amino derivative was dissolved in acetone (100 ml)-methanol (100 ml), followed by additon of a 47% aqueous HBr solution (22 g). A solution of $NaNO_2$ (2.4 g) in water (8 ml) was added dropwise to the solution at a temperature of not higher than 5°C. After the solution was stirred at 5°C for 15 minutes, methyl acrylate (16.3 g) was added, and the reaction mixture was warmed to 38°C. Powdered cuprous oxide (1 g) was added in small portions to the mixture with vigorous stirring. After stirring was continued until evolution of nitrogen gas stopped, the reaction mixture was concentrated. The residue was made basic with aqueous ammonia, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentated to give methyl 2-bromo-3-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl}propionate as a crude oily material (12.6 g, 88.7%).
IR (neat) cm^{-1}: 1735. NMR δ (ppm) in $CDCl_3$: 2.33 (3H, s), 2.93 (2H, t, J=7Hz), 3.0 to 3.5 (2H, m), 3.65 (3H, s), 4.0 to 4.4 (3H, m), 6.6 to 7.2 (4H, m), 7.4 (3H, m), 7.9 (2H, m).

2) Thiourea (2.1 g) and sodium acetate (2.3 g) were added to a solution of the oily material (12.4 g) as obtained in 1) in ethanol (100 ml), and the mixture was stirred under reflux for 3 hours. The reaction mixture was concentrated, and the residue was neutralized with aqueous saturated sodium bicarbonate solution, followed by addition of ether (50 ml)-hexane (50 ml). After stirring for 10 minutes, the crystals which separated out were collected by filtration to give 2-imino-5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-benzyl}-4-thiazolidinone (6.1 g, 53.5%). Recrystallization from ethanol afforded colorless prisms, m.p. 212—213°C. Elemental analysis for $C_{22}H_{21}N_3O_3S$; Calcd.: C, 64.85; H, 5.19; N, 10.31. Found: C, 64.85; H, 5.00; N, 10.25.

By a procedure similar to the above-described one, there were obtained the compounds as shown in Table 7. The yeild is expressed in terms of an over-all yield based on the starting nitro derivative.

Table 7:



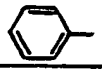
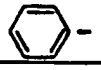
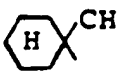
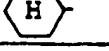
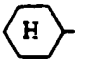
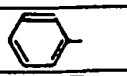
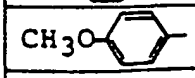
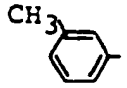
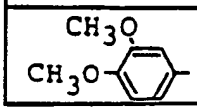
R^1	R^2	X	Melting point, °C	Recrystallizing solvent	Yield %
CH_3	H	S	185-186	Methanol	28.4
CH_3	H	O	202-204	Methanol-dichloromethane	46.6
	H	S	182-183	Methanol	44.9
	H	O	211-213	Methanol-dichloromethane	42.3
CH_3	CH_3	O	239-240	Methanol-dichloromethane	56.0
	CH_3	O	180-181	Ethanol	51.6
C_3H_7	H	O	175-176	Methanol	38.3
	H	S	182-184	Methanol	32.1
	H	O	203-205	Methanol-dichloromethane	38.4

Table 7 (continued)

R^1	R^2	X	Melting point, °C	Recrystallizing solvent	Yield %
C_2H_5	H	S	168-169	Methanol	46.9
i-C_3H_7	H	S	172-173	Methanol-dichloromethane	42.5
	C_2H_5	O	190-191	Ethanol	23.7
	CH_3	O	213-214	Ethanol	53.5
CH_3	C_2H_5	O	208-209	Ethanol-chloroform	33.8
	CH_3	O	171-172	Ethanol-water	38.8
	CH_3	O	222-224	Methanol-dichloromethane	41.0
	CH_3	O	194-195	Ethanol	45.0
	CH_3	O	197-198	Ethanol-chloroform	32.6

Reference Example 7

To a stirred solution of 4-acetyl-5-methyl-2-phenyloxazole (12.0g) in chloroform (100 ml) was added at 50°C a solution of bromine (10.5 g) in chloroform (10 ml). The mixture was further heated at 55°C for 30 minutes and poured into a saturated aqueous sodium bicarbonate solution (500 ml). The chloroform layer was separated and the aqueous layer was extracted with chloroform. The combined chloroform layer was washed with water and dried ($MgSO_4$). Evaporation of the solvent gave 4-bromoacetyl-5-methyl-2-phenyloxazole as crystals (14.5 g, 86.3%). Recrystallization from ethyl ether-hexane gave colorless rods, mp 88—89°C.

Reference Example 8

1) A mixture of 4-bromoacetyl-5-methyl-2-phenyloxazole (33.8 g), p-hydroxyacetanilide, potassium carbonate (27.6 g) and methyl ethyl ketone (400 ml) was stirred under reflux for 3 hours. The solvent was distilled off and 300 ml of water and ether (300 ml)-hexane (100 ml) were added to the residue. The mixture was stirred at room temperature for 10 minutes, and there were recovered by filtration the crystals (23.5 g, 58.3%) of 4-(4-acetamidophenoxyacetyl)-5-methyl-2-phenyloxazole which separated out. Recrystallization from ethanol afforded colorless prisms m.p. 175—176°C. Elemental analysis for $C_{20}H_{18}N_2O_4$; Calcd.: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.53; H, 5.15; N, 8.05.

2) 4-(4-acetamidophenoxyacetyl)-5-methyl-2-phenyloxazole (7.5 g) obtained in 1) was suspended in methanol (80 ml), and sodium borohydride (810 mg) was added portionwise to the suspension under ice-cooling. The mixture was stirred for 30 minutes. After acetic acid (2 ml) was added, the solution was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated to give 4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-acetanilide (6.8 g, 90.7%). Recrystallization from ethyl acetate afforded colorless needles, m.p. 166—167°C. Elemental analysis for $C_{20}H_{20}N_2O_4S$; Calcd.: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.26; H, 5.65; N, 8.11.

3) A mixture of 4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]acetanilide (11.5 g), 4N—KOH (100 ml) and ethanol (100 ml) was heated under reflux for 24 hours. The reaction solution was poured into water, and the crystals which separated out were collected by filtration and recrystallized from ethanol to give 4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]aniline (9.67 g, 96.0%) as colourless prisms, m.p. 139—140°C. Elemental analysis for $C_{18}N_{18}N_2O_3$; Calcd.: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.43; H, 5.76; N, 8.95.

4) 4-[2-Hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]aniline (18.5 g) was dissolved in methanol (50 ml)-acetone (150 ml), and 47% aqueous HBr (41.9 g) was added to the solution. Then, a solution of $NaNO_2$ (4.5 g) in water (10 ml) was added dropwise to the mixture at a temperature of not higher than 5°C. The whole was stirred at 5°C for 15 minutes, and methyl acrylate (30.4 g) was added to the mixed solution, followed by warming at 38°C. Cuprous oxide (2.0 g) was added in small portions to the reaction solution with vigorous stirring, and stirring was continued until evolution of nitrogen gas stopped. After

concentration, the residue was made basic with aqueous ammonia, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) concentrated to give methyl 2-bromo-3-{4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl}propionate as a crude oily material (27.0 g, 98.5%). IR (Neat) cm^{-1}: 3300, 1735. NMR δ (ppm) in $CDCl_3$: 2.04 (3H, s), 3.0 (1H, broad), 3.11 (1H, d.d, J = 14 and 7Hz), 3.39 (1H, d.d, J = 14 and 7Hz), 3.68 (3H, s), 4.0 to 4.5 (3H, m), 5.05 (1H, d.d, J = 8 and 5Hz), 6.0 to 7.2 (4H, m), 7.4 (3H, m), 7.9 (2H, m).

5) The oily material (27.0 g) obtained in 4) was dissolved in ethanol (270 ml), and thiourea (4.5 g) and sodium acetate (48 g) were added to the solution. The mixture was stirred under reflux for 4 hours and concentrated. The residue was neutralized with aqueous saturated sodium bicarbonate solution. Water (300 ml)-ether (200 ml) was added to the mixture, followed by stirring at room temperature for 30 minutes. The crystals which separated out were collected by filtration to give 2-imino-5-{4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-4-thiazolidinone (13.5 g, 54.0%). Recrystallization from methanol-chloroform afforded colorless needles, m.p. 238—239°C. Elemental analysis for $C_{22}H_{21}N_3O_4S$; Calcd. C, 62.40; H, 5.00; N, 9.92. Found: C, 62.24; H, 4.77; N, 9.79.

Reference Example 9

By a procedure similar to that of Reference Example 8, there were obtained the following compounds.

1) 4-(4-Acetamidophenoxyacetyl)-2,5-dimethyloxazole: m.p. 223—224°C. Yield 55.9%.

2) 4-[2-(2,5-Dimethyl-4-oxazolyl)-2-hydroxyethoxy]acetanilide: m.p. 157—158°C. Yield 93.3%.

3) 4-[2-(2,5-Dimethyl-4-oxazolyl)-2-hydroxyethoxy]aniline: Oily material. IR (Neat) cm^{-1}: 3300 (broad). Yield 99.1%.

4) 2-Imino-5-{4-[2-hydroxy-2-(5-dimethyl-4-oxazolyl)ethoxy]benzyl}-4-thiazolidinone: m.p. 238—239°C. Yield: 54.0%.

Reference Example 10

A mixture of 4-chloromethyl-5-methyl-2-phenyloxazole (12.0 g), p-hydroxyacetanilide (13.1 g), potassium carbonate (16.6 g) and DMF (150 ml) was stirred at 110°C for 3 hours and poured into water. The aqueous mixture was extracted with ethyl acetate and the ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated to five 4-(5-methyl-2-phenyl-4-oxazolylmethoxy)acetanilide (18.0 g, 95.7%). Recrystallization from ethanol afforded colorless plates, m.p. 154—155°C. Elemental analysis for $C_{19}H_{18}N_2O_3$: Calcd.: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.67; H, 5.57; N, 8.58.

2) A mixture of 4-(5-methyl-2-phenyl-4-oxazolylmethoxy)acetanilide (17.5 g) obtained in 1), 4H·KOH (150 ml) and ethanol (150 ml) was heated under reflux for 20 hours, and concentrated to about 1/2 of the original volume. The crustals which separated out were collected by filtration to give 4-(5-methyl-2-phenyl-4-oxazolylmethoxy)anilide (14.7 g, 96.7%). Recrystallization from ethanol afforded colorless prisms, m.p. 129—130°C. Elemental analysis for $C_{17}H_{16}N_2O_2$; Calcd.: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.79; H, 5.70; N, 9.87.

3) 4-(5-methyl-2-phenyl-4-oxazolylmethoxy)acetaniline (14.5 g) obtained in 2) was subjected to reactions similar to those in Reference Example 8—4) and 5) to give 2-imino-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyl]-4-thiazolidinone (11.8 g, 57.3%). Recrystallization from chloroform-methanol afforded colorless plates, m.p. 257—258°C. Elemental analysis for $C_{21}H_{19}N_3O_3S$; Calcd.: C, 64.11; H, 4.87; N, 10.68. Found: C, 64.16; H, 4.80; N, 10.80.

Reference Example 11

1) Reduced iron (10.6 g) was added portionwise mixture of 4-{2-[2-chlorophenyl)-5-methyl-4-oxazolyl]-ethoxy}nitrobenzene (22.9 g), acetic acid (150 ml) and water (50 ml) at 70°C. After stirring at 80°C for 2 hours, the insoluble matter was filtered off, and the filtrate was concentrated under reduced pressure. Water was added to the filtrate, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated to give 4-{2-(2-chlorophenyl)-5-methyl-4-oxazolyl]ethoxy}aniline as a crude oily material (20.5 g, 97.6%). NMR δ ppm in $CDCl_3$: 2.35 (3H, s), 2.93 (2H, t, J = 7Hz), 3.77 (2H, s), 4.15 (2H, t, J = 7Hz), 6.56 (2H, d, J = 9Hz), 6.75 (2H, d, J = 9Hz), 7.2 to 7.5 (3H, m), 7.9 (1H, m).

2) The oily material (20.5 g) obtained in 1) was dissolved in acetone (100 ml)-methanol (100 ml), and 47% aqueous HBr (45 g) was added to the solution. Then, a solution of $NaNO_2$ (4.8 g) in water (10 ml) was added dropwise thereto at a temperature of not higher than 5°C. After stirring at 5°C for 15 minutes, methyl acrylate (33 g) was added to the mixture and the whole was warmed to 38°C. Cuprous oxide (2 g) was added in small portions to the mixture with vigorous stirring, and stirring was continued until evolution of nitrogen gas stopped. The reaction solution was concentrated under reduced pressure and the residue was made basic with aqueous ammonia, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated to give methyl 2-brom -3-<4-{2-[2-(2-chl r phenyl)-5-methyl-4-oxazolyl]ethoxy}phenyl>-pr pionate as a crude oily material (24.5 g). NMR (ppm) in $CDCl_3$: 2.37 (3H, s), 2.97 (2H, t, J − 7Hz), 3.12 (1H, d.d, J − 14 and 7Hz), 3.38 (1H, d.d, J − 14 and 7Hz), 4.1 to 4.4 (3H, m), 6.7 to 7.5 (7H, m), 7.9 (1H, m).

3) The oily material (24.5 g) obtained in 2) was dissolved in ethanol (250 ml), and thiourea (4.9 g) and sodium acetate (5.2 g) w re added to the soluti n. The mixture was heated under reflux f r 10 hours, and c ncentrated. Water was poured onto the residue, and the crystals which separated out were c llected by

filtrati n. Recrystallization from ethanol-dichloromethane gave 5-<4-{2-[2-(2-chlorophenyl)-5-methyl-4-oxazolyl]eth xy}-benzyl>-2-imino-4-thiazolidinon (9.6 g, 34.1%), m.p. 174—176°C. Elem ntal analysis for $C_{22}H_{10}N_3O_3SCl$; Calcd.: C, 59.79; H 4.56; N, 9.51. Found: C, 59.69; H, 4.60; N, 9.34.

Reference Example 12

By a procedure similar to that of Reference Example 11, there were obtained crystals (yield; 53.1% based on the corresponding nitro derivative) of 2-imino-5-<4-{2[5-methyl-2-(2-thienyl)-4-oxazolyl]ethoxy}-benzyl>-4-thiazolidinone. Recrystallization from methanol-dichloromethane afforded colorless prisms, m.p. 171—172°C. Elemental analysis for $C_{20}H_{19}N_3O_3S_2$; Calcd.: C, 58.09; H, 4.63; N, 10.16. Found: C, 57.86; H, 4.59; H, 10.04.

Reference Example 13

1) A solution of 4-{2-[2-(4-benzyloxyphenyl)-5-methyl-4-oxazolyl]ethoxy}nitrobenzene (10.65 g) in methanol (200 ml) was subjected to a catalytic hydrogenation over 10% Pd—C (50% wet, 4.0 g). After the catalyst was filtered off, the filtrate was concentrated to give 4-{2-[2-(4-hydroxyphenyl)-5-methyl-4-oxazolyl]ethoxy}aniline (6.21 g, 78.2%). Recrystallization from methanol afforded brownish prisms, m.p. 184—185°C. Elemental analysis for $C_{18}H_{18}N_2O_3$; Calcd.: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.69; H, 5.87; N, 9.01.

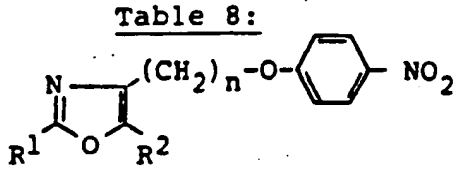
2) The crystals (6.11 g) obtained in 1) were dissolved in acetone (40 ml)-methanol (20 ml), and 47% aqueous HBr (7.7 ml) was added to the solution. Then, a solution of $NaNO_2$ (1.44 g) in water (3 ml) was added dropwise to the mixture at a temperature of not higher than 5°C. After stirring at 5°C for 15 minutes, methyl acrylate (12 ml) was added to the mixed solution, and the whole was warmed to 38°C. Powdered cuprous oxide (1 g) was added in small portions to the mixture with vigorous stirring. After stirring was continued until evolution of nitrogen gas stopped, the reaction mixture was concentrated. The residue was made basic by aqueous ammonia and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated to give crude crystals of methyl 2-bromo-3-<4-{2-[2-(4-hydroxyphenyl)-5-methyl-4-oxazolyl]ethoxy}phenyl>propionate.

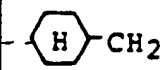
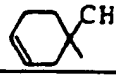
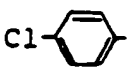
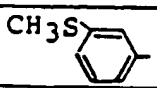
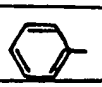
3) The whole amount of the crystals obtained in 2) was dissolved in ethanol (100 ml), and thiourea (2.28 g) and sodium acetate (2.46 g) were added to the solution. The mixture was stirred under reflux for 2 hours. The reaction mixture was poured into water, and the crystals which separated out were collected by filtration and washed with water and ether successively. Recrystallization from methanol and dichloromethane yielded 2-imino-5-<4-{2-[2-(4-hydroxyphenyl)-5-methyl-4-oxazolyl]ethoxy}benzyl>4-thiazolidinone (5.35 g, 66.5%), colorless prisms, m.p. 175—177°C. Elemental analysis for $C_{22}H_{21}N_3O_4S \cdot 1/2H_2O$; Calcd.: C, 61.10; H, 5.13; N, 9.72. Found: C, 61.02; H, 4.92; N, 9.56.

Reference Example 14

By a procedure similar to that of Reference Example 5, there were obtained the compounds shown in Table 8.

Table 8:



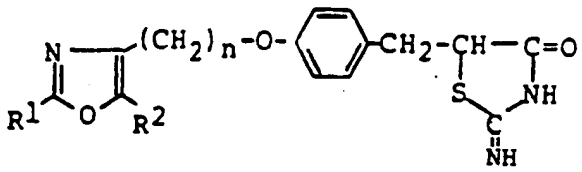
n	R^1	R^2	Melting point, °C	Recrystallizing solvent	Yield %
2		CH_3	Oily material	-	80.3
2		CH_3	"	-	80.8
2		CH_3	153-154	Ethyl acetate	94.7
2		CH_3	104-105	Methanol	87.5
2		CH_3	112-113	Ethyl acetate-hexane	92.4
3		CH_3	111-112	Ethyl acetate-hexane	90.0

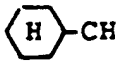
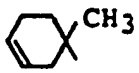
Reference Example 15

By a procedure similar to that of Reference Example 6, there were obtained the c mp unds shown in Table 9.

(The yield is expressed in terms of an over-all yield based on the starting nitro derivative).

Table 9:



n	R^1	R^2	Melting point, °C	Recrystallizing solvent	Yield %
2		CH_3	180-182	Methanol	41.7
2		CH_3	136-138	Ethyl acetate	37.3
3		CH_3	179-180	Ethanol	36.1

Reference Example 16

By a procedure similar to that of Reference Example 8, there was obtained the following compounds.

1) 4-(4-Acetamidophenoxyacetyl)-2-cyclohexyl-5-methyloxazole: m.p. 158—159°C. Yield 48.1%.

2) 4-[2-(2-Cyclohexyl-5-methyl-4-oxazolyl)-2-hydroxyethoxy]-acetanilide: m.p. 125—126°C. Yield 98.4%.

3) 4-[2-(2-Cyclohexyl-5-methyl-4-oxazolyl)-2-hydroxyethoxy]-aniline: Oily material. IR (neat) cm^{-1}: 3350 (broad). Yield 98.1%.

4) 5-{4-[2-Cyclohexyl-5-methyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-2-imino-4-thiazolidinone: m.p. 167—168°C. Yield of 34.4%.

Reference Example 17

By a procedure similar to that of Reference Example 11, there was obtained the following compounds.

1) 4-{2-[2-(4-Chlorophenyl)-5-methyl-4-oxazolyl)ethoxy}aniline: m.p. 145—146°C. Yield 59.9%.

2) Methyl 2-bromo-3-<4-{2-[2-(4-chlorophenyl)-5-methyl-4-oxazolyl]ethoxy}phenyl>propionate: Oily material. IR (Neat) cm^{-1}: 1740. Yield 92.7%.

3) 5-<-{2-[2-(4-chlorophenyl)-5-methyl-4-oxoazolyl]ethoxy}-benzyl>-2-imino-4-thiazolidinone: m.p. 238—239°C. Yield 49.5%.

Reference Example 18

1) A solution of 4-{2-[5-methyl-2-(3-methylthiophenyl)-4-oxazolyl]ethoxy}nitrobenzene (8.8 g) in methanol (100 ml) was subjected to catalytic hydrogenation over 10% Pd—C (50% wet, 10 g), and the catalyst was filtered off to give 4-{2-[5-methyl-2-(3-methylthiophenyl)-4-oxazolyl]ethoxy}aniline (5.9 g, 72.8%). Recrystallization from ethyl acetate-hexane afforded colorless prisms, m.p. 110—111°C. Elemental analysis for $C_{19}H_{20}N_2O_2S$; Calcd.: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.20; H, 5.94; N, 8.12.

2) The crystals obtained in 1) was subjected to reactions similar to those in Reference Example 13—2) and 3) to give 2-imino-5-<4-{2-[5-methyl-2-(3-methylthiophenyl)-4-oxazolyl]ethoxy}benzyl>-4-thiazolidinone. Recrystallization from ethyl acetate-methanol afforded colorless prisms, m.p. 182—183°C. Elemental analysis for $C_{23}H_{23}N_3O_3S_2$; Calcd.: C, 60.91; H, 5.11; N, 9.26. Found: C, 60.42; H, 4.76; N, 9.06.

Reference Example 19

By a procedure similar to that of Reference Example 18, there were obtained the following compounds.

1) 4-{2-[5-methyl-2-(3-trifluoromethylphenyl)-4-oxazolyl)ethoxy}aniline: m.p. 121—122°C. Yield 97.5%.

2) 2-Imin -5-<4-{2-[5-methyl-2-(3-triflu r methylphenyl)-4-oxazolyl]ethoxy}benzyl>-4-thiazolidinone. m.p. 212—213°C. Yield 42.2%.

Reference Example 20

A s lution of (Z)-5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)eth xy]benzylidene}-2,4-thiazolidin di ne (200 mg) in acetonitrile (750 ml), in a quartz tube under a stream of nitrogen, was irradiated by a 300 W high-pressure mercury lamp for 3 hours. The solvent was distilled off, and the resulting crystals were chromatographed n a column of silica gel (200 g). Elution with hexane-ethyl acetate (1:1, V/V) gav (E)-5-

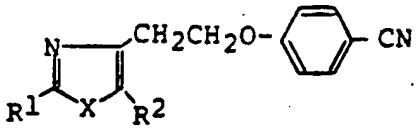
{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-thiazolidinedione (40 mg, 20.0%). Recrystallization from dichloromethane-ethanol yielded colorless needl s, m.p. 216—217°C. Elemental analysis for $C_{22}H_{18}N_2O_4S$; Calcd.: C, 65.01; H, 4.46; N, 6.89. F und: C, 64.69; H, 4.26; N, 7.11. The subsequent elution with hexane-ethyl acetate (1:1, V/v) allowed the recovery of (Z)-5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene}-2,4-thiazolidinedione (138 mg, 69.0%).

Reference Example 21

2-(5-methyl-2-phenyl-4-oxazolyl)ethanol (6.0 g) and 4-fluorobenzonitrile (5.4 g) were dissolved in tetrahydrofurane (70 ml), and 60% sodium hydride in oil (1.4 g) was added to the solution under ice-cooling with vigorous stirring. The reaction mixture was stirred at room temperature for 18 hours and poured into ice-cold water (0.5 l). The aqueous mixture was neutralized with acetic acid, and the crystals which separated out were collected by filtration to give 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzonitrile (7.0 g, 77.5%). Recrystallization from ether-hexane afforded colorless prisms, m.p. 119—120°C. Elemental analysis for $C_{19}H_{16}N_2O_2$; Calcd: C, 74.88; H 5.30; N, 9.20. Found: C, 74.90; H, 5.01; N, 9.28.

By a procedure similar to the above, there were obtained the compounds shown in Table 10.

Table 10:



R^1	R^2	X	Melting point, °C	Recrystallizing solvent	Yield %
CH_3	H	S	75.5-76.5	Ether-hexane	57.7
	H	S	90-91	Ether-hexane	67.8
	C_2H_5	O	128.5-130	Ether-hexane	65.8
	CH_3	O	105-106	Ether	59.6
	CH_3	O	134-135	Ether-hexane	74.9
	CH_3	O	110-111.5	Ether-hexane	83.1
	CH_3	O	128-129	Acetone-hexane	90.3
	CH_3	O	89-91	Ether-hexane	74.8
	CH_3	O	Oily material	-	59.7
	CH_3	O	Oily material	-	42.6

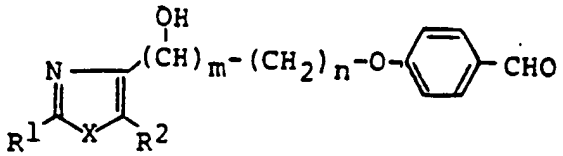
Reference Example 22

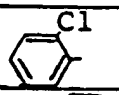
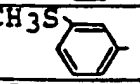
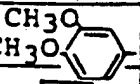
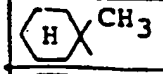
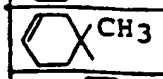
A mixture of 4-[2-(5-methyl-2-ph nyl-4-oxaz lyl)-ethoxy]benzonitrile (6.5 g), Ran y nickel all y (6.5 g) and 70% formic acid (100 ml) was heated under reflux for 2 hours. The insoluble matter was filtered off, and the filtrate was concentrated under reduced pressure. Water was added t the residue, and the mixture was extracted with thyl ac tate. The thyl acetate layer was washed with wat r, dried ($MgSO_4$) and concentrated. The remaining oily material was chromatographed n a coloumn of silica gel, and from the

fractions eluted with chlor form-hexane (1:1, V/V), there were obtained crystals (5.2 g, 78.5%) of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzaldehyde. Recrystallization from ether-hexane yielded col rless needles, m.p. 82—84°C. Elemental analysis for $C_{19}H_{17}NO_3$; Calcd.: C, 74.25; H, 5.57; N, 4.56. F und: C, 74.47; H, 5.53; N, 4.34.

By a procedure similar to the above, there were obtained the compounds shown in Table 11.

Table 11:



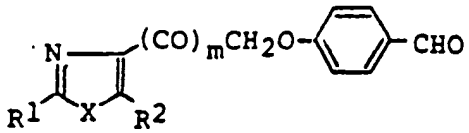
R^1	R^2	X	m	n	Melting point, °C	Recrystallizing solvent	Yield %
CH_3	H	S	0	2	69-70	Ether-hexane	75.5
	H	S	0	2	60-61	Ether-hexane	71.4
	C_2H_5	O	0	2	Oily material	-	85.2
	CH_3	O	0	2	74-75	Ether-hexane	81.0
	CH_3	O	0	2	113-114	Ether-hexane	59.5
	CH_3	O	0	2	81-82	Ether-hexane	54.5
	CH_3	O	0	2	85-89	Ether	70.3
	CH_3	O	0	2	Oily material	-	95.5
	CH_3	O	0	2	75-76	Ether-hexane	80.6
	CH_3	O	0	2	Oily material	-	68.2
	CH_3	O	1	1	136-137	Acetone	71.1

Reference Example 23

A mixture of 4-chloromethyl-5-methyl-2-phenyloxazole (3.12 g), 4-hydroxybenzaldehyde (1.83 g), potassium carbonate (2.28 g) and dimethylformamide (40 ml) was stirred under heating at 110°C for 1 hour. The reaction solution was poured into ice-cold water, and the crystals which separated out were collected by filtration to give 4-(5-methyl-2-phenyl-4-oxazolyl)methoxybenzaldehyde (4.40 g, 99.8%). Recrystallization from ether-hexane yielded colorless prisms, m.p. 112—113°C. Elemental analysis for $C_{115}H_{15}NO_3$; Calcd.: C, 73.71; H, 5.15; N, 4.87. Found: C, 73.87; H, 5.26; N, 4.81.

By a procedure similar to the above, there were obtained the compounds shown in Table 12.

Table 12:



R^1	R^2	X	m	Melting point, °C	Recrystallizing solvent	Yield %
	H	S	0	88-89	Ether-hexane	94.7
	H	O	0	99.5-100.5	Acetone-hexane	88.7
	CH_3	O	1	175-177	Chloroform-ethanol	80.4
CH_3	CH_3	O	1	130.5-132	Ethanol	94.3

Reference Example 24

A mixture of 4-bromoacetyl-5-methyl-2-phenyloxazole (7.0 g), p-cyanophenol (3.0 g), potassium carbonate (6.9 g) and methyl ethyl ketone (100 ml) was heated under reflux for 2 hours. The reaction mixture was concentrated under reduced pressure, and water (100 ml)-ether (100 ml) was added to the residue. The mixture was stirred, and the crystals were collected by filtration. Recrystallization from chloroform-ethanol afforded 4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzonitrile (6.3 g, 78.8%), as brownish prisms, m.p. 202—203°C.

Reference Example 25

Sodium borohydride (0.654 mg) was added to a suspension of 4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-oxoethoxy]benzonitrile (5.5 g) in methanol (100 ml)-N,N-dimethylformamide (50 ml), followed by stirring at room temperature for 1 hour. The reaction solution was poured into water and the crystals which separated out were collected by filtration to give 4-[2-hydroxy-2-(5-methyl-phenyl-4-oxazolyl)ethoxy]-benzonitrile (5.1 g, 92.7%). Recrystallization from acetone afforded colorless needles, m.p. 176—177°C.

Experiment Example

Blood glucose and plasma lipid lowering actions in mice:

Test compounds were given to KKA^y-mice (male, 8 to 10 weeks old, groups of 5 mice each) as a dietary admixture of 0.001% or 0.005% in CE-2 powdered diet (CLEA Japan Inc., Tokyo) for 4 days. The animals were allowed free access to diet and water. Blood samples were taken from the orbital venous plexuses of the mice. Blood glucose was measured by a glucose oxidase method and plasma triglyceride (TG) was enzymatically determined using a commercially available assay kit, Cleantech TG—S kit (Iatron). The respective measurements were used for calculation in accordance with the following equation. The results are shown in Table 13, in which the data obtained with a known compound having similar chemical structure are given for comparison.

$$\frac{\left(\begin{array}{c}\text{measurement for the}\\ \text{control group}\end{array}\right) - \left(\begin{array}{c}\text{measurement for the}\\ \text{treated group}\end{array}\right)}{\text{(measurement for the control group)}} \times 100$$

Table 13:

Compound (Example No.)	Blood-glucose lowering action (%)		TG lowering action (%)	
	0.001 %	0.005 %	0.001 %	0.005 %
1	-	48****	-	51***
2	-	28***	-	32*
6	23***	41****	17**	44****
7	-	25**	-	30**
8	-	21**	-	35*
12	55****	59****	67****	66****
14	-	42****	-	52***
15	-	37****	-	42***
16	39****	52****	54***	63***
17	41****	58****	51**	68***
18	-	55****	-	56****
19	-	52****	-	65****
20	-	55****	-	37***
21	-	56****	-	45
22	54****	58****	62****	81****
23	49****	55****	55****	79****
24	53****	55****	63****	72****
25	-	46****	-	45***
26	50****	50****	41****	69****
27	50****	51****	41****	72****
28	55****	51****	52****	62****
34	21***	53****	23	54****
37	51****	52****	58****	71****
47	50****	55****	65****	67****
50	41****	57****	41***	57****
52	-	54****	-	59****
53	-	31****	-	30**
55	-	52****	-	58****
57	-	55****	-	57****
58	-	33*	-	29
59	36****	56****	54***	60****
63	-	66****	-	51****
64	26****	59****	37*	61 ***
Control compound: Ciglitazone [1)]	-	10	-	-13

t-test; *P 0.05, **P 0.02, ***P 0.01, ****P 0.001

1) 5-[4-(1-Methylcycl hexylmethoxy)]benzyl-2,4-thiazolidin dion .

(Results)

As is bvious from Table 13, the comp unds of this invention demonstrated statistically significant bl od-glucose r/and GT lowering actions, whereas the contr l compound, at the dos employed in this experiment, failed to exhibit any significant action.

Tablet Production Example

a) (1) 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl) ethoxy]benzyl}-2,4-thiazolidinedione	10 g
(2) Lactose	50 g
(3) Corn starch	15 g
(4) Carboxymethylcellulose calcium	44 g
(5) Magnesium stearate	1 g
	120 g for 1000 tablets

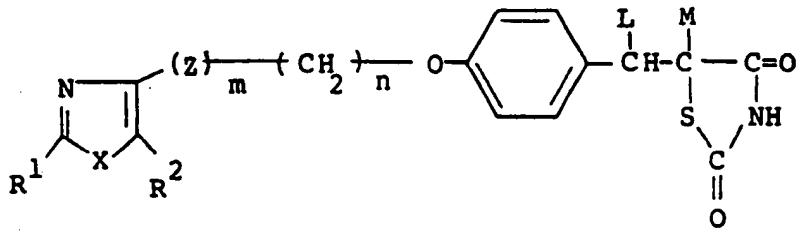
The whole amount each of the ingredients (1), (2) and (3) as well as 30 g of the ingredient (4) are kneaded with water, and the mixture was dried under vacuum and granulated. The resulting granules are mixed with 14 g of the ingredient (4) and 1 g of the ingredient (5), and the mixture is compressed into tablets by a tabletting machine to prepare 1000 tablets each containing 10 mg of the ingredient (1).

b) (1) 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl) ethoxy]benzylidene}-2,4-thiazolidinedione	30 g
(2) Lactose	50 g
(3) Corn starch	15 g
(4) Carboxymethylcellulose calcium	44 g
(5) Magnesium stearate	1 g
	140 g for 1000 tablets

The whole amount each of the ingredients (1), (2) and (3) as well as 30 g of the ingredient (4) are kneaded with water, and the mixture is dried under vacuum and granulated. The resulting granules are mixed with 14 g of the ingredient (4) and 1 g of the ingredient (5), and the mixture is compressed into tablets by a tabletting machine to prepare 1000 tablets each containing 30 mg of the ingredient (1).

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the general formula:



wherein

R^1 is hydrogen, a hydrocarbon residue having 1 to 13 carbon atoms, r a five- or six-membered ring containing, in addition to carbon, 1 to 3 atoms selected from N, O and S as a ring-forming at m and capable of bonding through carbon, and each of said hydrocarbon residue and said ring may be substituted by 1 to 3 substituents selected from alkyl having 1 to 3 carbon atoms when R^1 includes a alicyclic group or is a saturated heterocyclic group, or by 1 to 4 substituents selected from halogen, hydr xyl, cyano, trifluoromethyl, alk xy having 1 to 4 carb n at ms, alkyl having 1 to 4 carbon at ms, alkoxycarbonyl having 2 to 4

carbon atoms and alkylthi having 1 to 3 carbon atoms wh n either R^1 includes aromatic hydrocarbon or R^1 is a heteroaromatic ring group;

R^2 is hydr gen or l wer alkyl having 1 to 5 carbon at ms which may be substituted by hydroxyl;

X is an oxygen or sulfur atom;

Z is a hydroxylated methylene or carbonyl;

m is 0 or 1;

n is an integer of 1 to 3;

L and M represent independently a hydrogen atom or L and M combine with each other to cooperate jointly to form a linkage, or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein the hydrocarbon residue represented by R^1 is an aliphatic hydrocarbon residue, an alicyclic hydrocarbon residue, an alicyclic-aliphatic hydrocarbon residue, an aromatic-aliphatic hydrocarbon residue or an aromatic hydrocarbon residue.

3. A compound as claimed in claim 1, wherein the heterocyclic reside is a heteroaromatic ring group or a saturated heterocyclic group.

4. A compound as claimed in claim 1, wherein R^1 is an alicyclic hydrocarbon residue, and alicyclic-aliphatic hydrocarbon residue or a saturated heterocyclic group, each of which may be substituted by a lower alkyl of 1 to 3 carbon atoms.

5. A compound as claimed in claim 1, wherein R^1 is an aromatic-aliphatic hydrocarbon residue, aromatic hydrocarbon residue and heteroaromatic ring group, each of which may be substituted by a halogen, hydroxyl, cyano, trifluoromethyl, an alkoxy having 1 to 4 carbon atoms, an alkyl having 1 to 4 carbons atoms, a alkoxycarbonyl having 2 to 4 carbon atoms or an alkylthio having 1 to 3 carbon atoms.

6. A compound as claimed in claim 1, wherein R^2 is an alkyl having 1 to 5 carbon atoms.

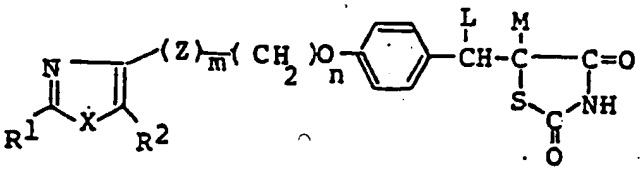
7. A compound as claimed in claim 1, wherein m is 1 and Z is hydroxymethylene.

8. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-methyl-2-phenyl-4-oxazoyl)-ethoxy]benzylidene}-2,4-thiazolidinedione.

9. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-2,4-thiazolidinedione.

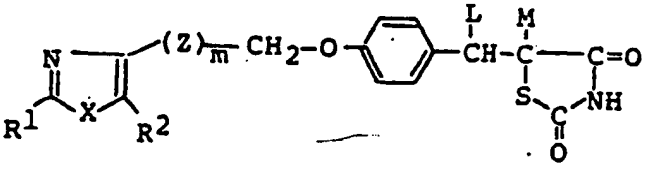
10. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-thiazolidinedione.

11. A pharmaceutical composition which contains a thiazolidinedione derivative of the general formula:

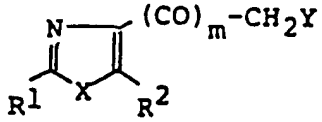


as defined in claim 1, or a pharmaceutically acceptable salt thereof.

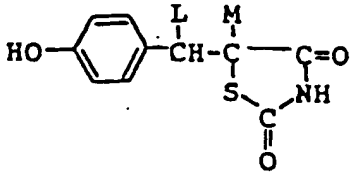
12. A process for producing a compound of the general formula:



where the symbols are as defined in claim 1, or its salts, which comprises reacting a compound of the general formula:

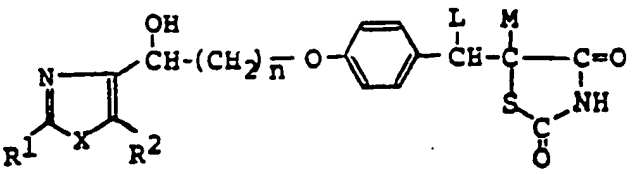


[wherein Y is a halogen atom and the other symbols are as defined in claim 1] with a compound of the general formula:

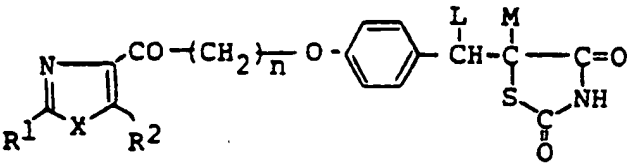


[wherein L and M are as defined in claim 1] or its salt, followed by reduction of the reaction product, if desired.

13. A process for producing a compound of the general formula:

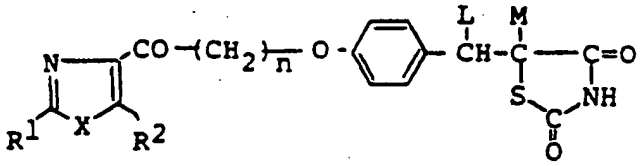


where the symbols are as defined in claim 1, or its salt, which comprises reducing a compound of the general formula:

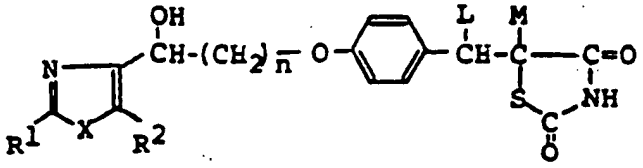


[wherein each of the symbols is as defined in claim 1] or its salt.

14. A process for producing a compound of the general formula:

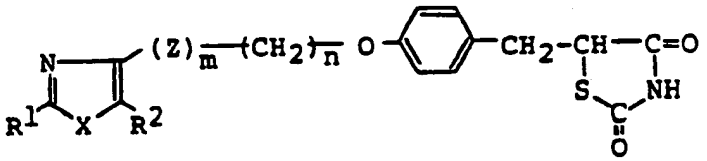


where the symbols are as defined in claim 1, or its salt, which comprises oxidizing a compound of the general formula:

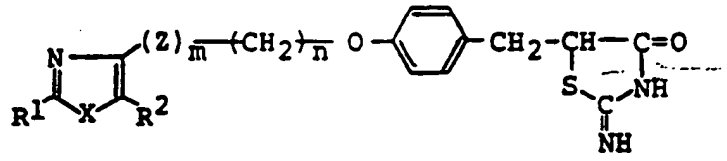


[wherein each of the symbols is as defined in claim 1] or its salt.

15. A process for producing a compound of the general formula:

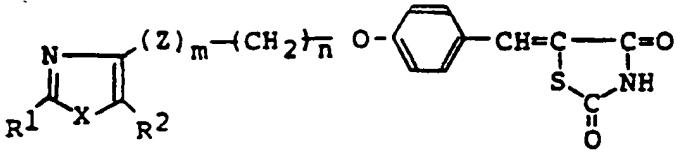


where the symbols are as defined in claim 1, or its salt, which comprises hydrolyzing a compound of the general formula:

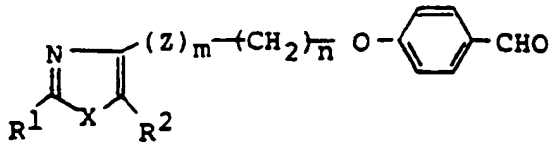


[wherein each of the symbols is as defined in claim 1] or its salt.

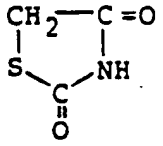
16. A process for producing a compound of the general formula:



where the symbols are as defined in claim 1, or its salt, which comprises reacting a compound of the general formula:

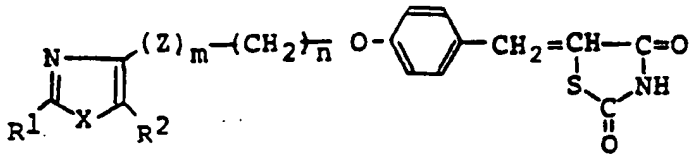


[wherein each of the symbols is as defined in claim 1] with a compound of the formula:

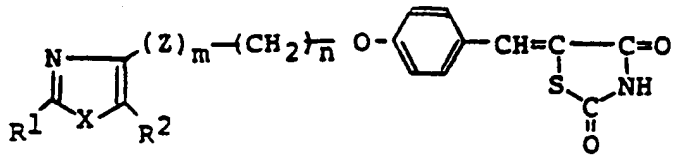


or its salt.

17. A process for producing a compoud of the general formula:



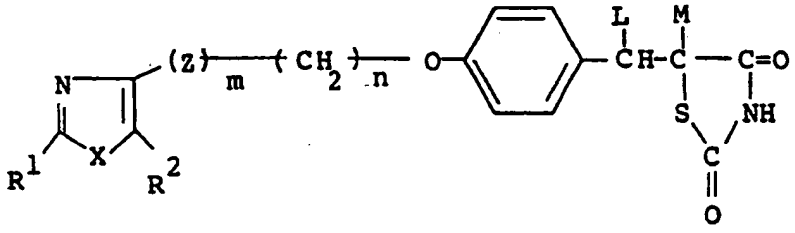
where the symbols are as defined in claim 1, or its salt which comprises reducing a compound of the general formula:



[wherein each of the symbols is as defined in claim 1].

Claims for Contracting State: AT

1. A process for producing a compound of the general formula:



wherein

R^1 is hydrogen, a hydrocarbon residue having 1 to 13 carbon atoms, or a five- or six-membered ring containing, in addition to carbon, 1 to 3 atoms selected from N, O and S as a ring-forming atom and capable of bonding through carbon, and each of said hydrocarbon residue and said ring may be substituted by 1 to 3 substituents selected from alkyl having 1 to 3 carbon atoms when R^1 includes an alicyclic group or is a saturated heterocyclic group, or by 1 to 4 substituents selected from halogen, hydroxyl, cyano, trifluoromethyl, alkoxy having 1 to 4 carbon atoms, alkyl having 1 to 4 carbon atoms, alkoxycarbonyl having 2 to 4 carbon atoms and alkylthio having 1 to 3 carbon atoms when either R^1 includes aromatic hydrocarbon or R^1 is a heteroaromatic ring group;

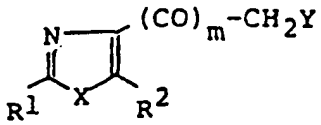
R^2 is hydrogen or lower alkyl having 1 to 5 carbon atoms which may be substituted by hydroxyl;

X is an oxygen or sulfur atom;

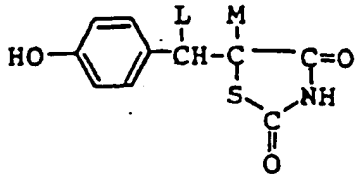
Z is a hydroxylated methylene or carbonyl;

m is 0 or 1;

L and M represent independently a hydrogen atom or L and M combine with each other to cooperate jointly to form a linkage, or its salt, which comprises reaching a compound of the general formula:

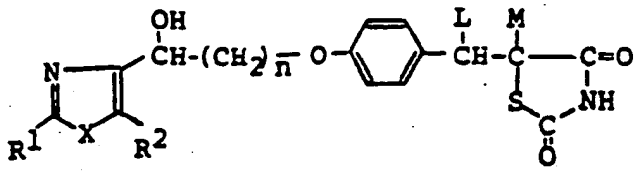


[wherein Y is a halogen atom and the other symbols are as defined hereinbefore] with a compound of the general formula:

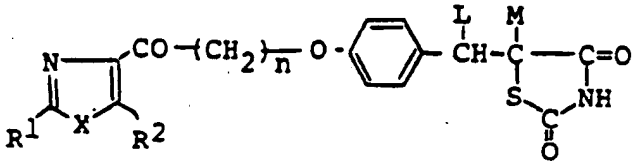


[wherein L and M are as defined hereinbefore] or its salt, followed by reduction of the reaction product, if desired.

2. A process for producing a compound of the general formula:

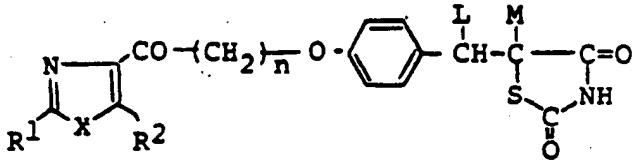


where the symbols are as defined in claim 1 and n is an integer of 1 to 3; or its salts, which comprises reacting a compound of the general formula:

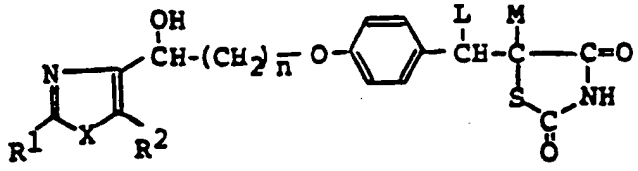


[wherein each of the symbols is as defined in claim 1] or its salt.

3. A process for producing a compound of the general formula:

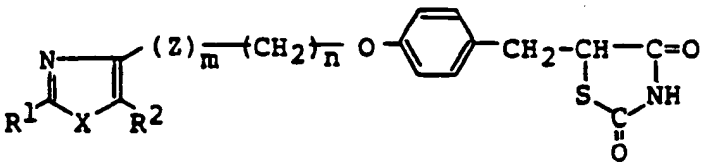


where the symbols are as defined in claim 2, or its salt, which comprises oxidizing a compound of the general formula:

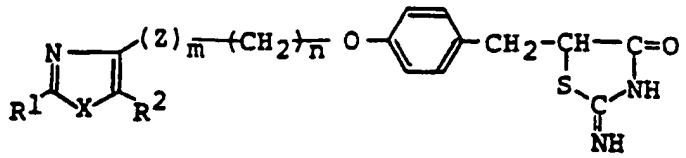


[wherein each of the symbols is as defined in claim 1] or its salt.

4. A process for producing a compound of the general formula:

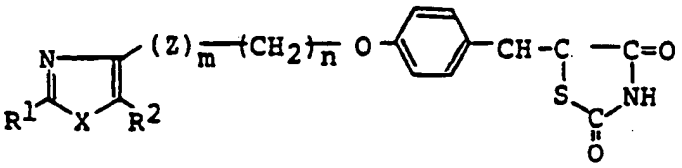


where the symbols are as defined in claim 1 and n is an integer of 1 to 3, r its salt, which comprises hydrolyzing a comp und of the general formula:

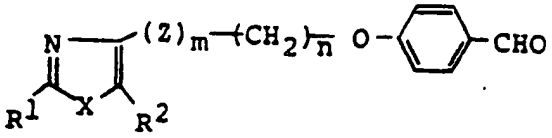


[wherein each of the symbols is as defined in claim 1] or its salt.

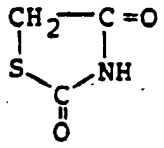
5. A process for producing a compound of the general formula:



where the symbols are as defined in claim 1 and n is an integer of 1 to 3, or its salt, which comprises reacting a compound of the general formula:

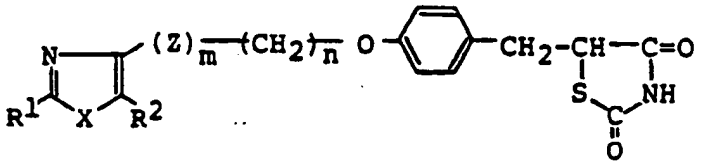


[wherein each of the symbols is as defined in claim 1] with a compound of the formula:

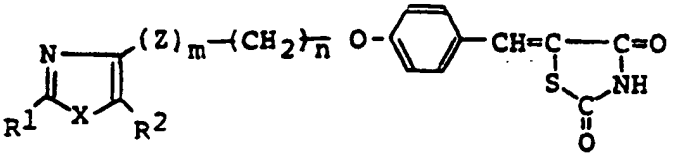


or its salt.

6. A process for producing a compound of the general formula:



where the symbols are as defined in claim 1 and n is an integer of 1 to 3, or its salt, which comprises a compound of the general formula:



[wherein each of the symbols is as defined in claim 1].

7. A process as claimed in any of claims 1 to 6, wherein the hydrocarbon residue represented by R^1 is an aliphatic hydrocarbon residue, an alicyclic hydrocarbon residue, an alicyclic-aliphatic hydrocarbon residue, an aromatic-aliphatic hydrocarbon residue or an aromatic hydrocarbon residue.

8. A process as claimed in any of claims 1 to 7, wherein the heterocyclic residue is a heterocyclic ring group or a saturated heterocyclic group.

9. A process as claimed in any of claims 1 to 8, wherein R^1 is an alicyclic hydrocarbon residue, an alicyclic-aliphatic hydrocarbon residue or a saturated heterocyclic group, each of which may be substituted by a lower alkyl of 1 to 3 carbon atoms.

10. A process as claimed in any of claims 1 to 9, wherein R^1 is an ar matic-aliphatic hydr carb n r sidue, aromatic hydrocarbon r sidue or heteroaromatic ring group, each of which may be substituted by a halogen, hydroxyl, cyano, triflu romethyl, an alkoxy having 1 to 4 carbon atoms, an alkyl having 1 t 4 carb n atoms, an alkoxycarb nyl having 2 to 4 carbon atoms or an alkylthi having 1 t 3 carbon atoms.

11. A process as claimed in any of claims 1 t 10, wherein R^2 is an alkyl having 1 to 5 carbon atoms.

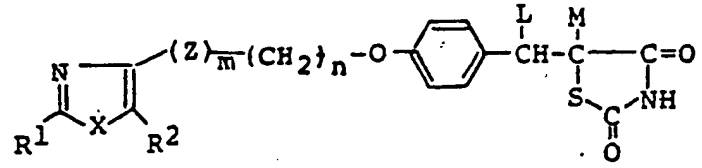
12. A process as claim d in any of claims 1 t 11, wherein m is 1 and Z is hydroxym thylene.

13. A process as claimed in claim 1, wherein the compound is 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]benzylidene}-2,4-thiazolidinedione.

14. A process as claimed in claim 1, wherein the compound is 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-2,4-thiazolidinedione.

15. A process as claimed in claim 1, wherein the compound is 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]benzyl}-2,4-thiazolidinedione.

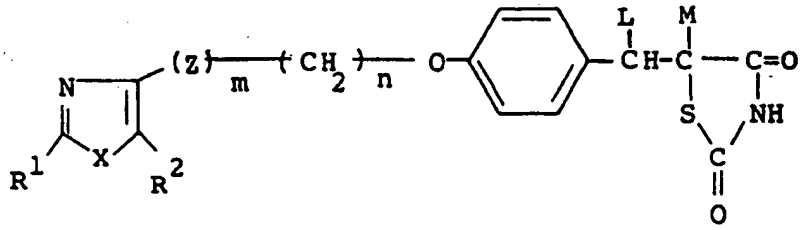
16. A pharmaceutical composition which contains a thiazolidinedione derivative of the general formula:



where the symbols are as defined in claim 1 and n is an integer of 1 to 3; or a pharmaceutically acceptable salt thereof.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung der allgemeinen Formel



worin

R^1 Wasserstoff, ein Kohlenwasserstoff-Rest mit 1 bis 13 Kohlenstoff-Atomen oder ein fünf- oder sechsgliedriger Ring ist, der neben Kohlenstoff 1 bis 3 aus N, O und S ausgewählte Atome als ringbildendes Atom enthält und zur Bindung über Kohlenstoff befähigt ist, und der Kohlenwasserstoff-Rest und der Ring jeweils durch 1 bis 3 Substituenten, die aus Alkyl mit 1 bis 3 Kohlenstoff-Atomen ausgewählt sind, wenn R^1 eine alicyclische Gruppe enthält oder eine gesättigte heterocyclische Gruppe ist, oder durch 1 bis 4 Substituenten, die aus Halogen, Hydroxyl, Cyano, Trifluoromethyl, Alkoxy mit 1 bis 4 Kohlenstoff-Atomen, Alkyl mit 1 bis 4 Kohlenstoff-Atomen, Alkoxycarbonyl mit 2 bis 4 Kohlenstoff-Atomen und Alkylthio mit 1 bis 3 Kohlenstoff-Atomen ausgewählt sind, wenn R^1 entweder einen aromatischen Kohlenwasserstoff umfaßt oder R^1 eine heteroaromatische Ring-Gruppe ist;

substituiert sein können,

R^2 Wasserstoff oder Niederalkyl mit 1 bis 5 Kohlenstoff-Atomen, das durch Hydroxyl substituiert sein kann, ist;

X ein Sauerstoff- oder Schwefel-Atom ist;

Z ein hydroxyliertes Methylen oder Carbonyl ist;

m 0 oder 1 ist;

n eine ganze Zahl von 1 bis 3 ist;

L und M unabhängig voneinander ein Wasserstoff-Atom darstellen oder so miteinander kombiniert sind, daß sie gemeinsam eine Bindung bilden,

oder ein pharmazeutisch annehmbares Salz derselben.

2. Verbindung nach Anspruch 1, worin der durch R^1 dargestellte Kohlenwasserstoff-Rest ein aliphatischer Kohlenwasserstoff-Rest, ein alicyclischer Kohlenwasserstoff-Rest, ein alicyclisch-aliphatischer Kohlenwasserstoff-Rest, ein aromatisch-aliphatischer Kohlenwasserstoff-Rest oder ein aromatischer Kohlenwasserstoff-Rest ist.

3. Verbindung nach Anspruch 1, worin der heterocyclische Rest eine heteroaromatische Ring-Gruppe oder eine gesättigte heterocyclische Gruppe ist.

4. Verbindung nach Anspruch 1, worin R^1 ein alicyclischer Kohlenwasserstoff-Rest, ein alicyclish-aliphatischer Kohlenwasserstoff-Rest oder eine gesättigte heterocyclisch Gruppe ist, die jeweils durch ein Niederalkyl mit 1 bis 3 Kohlenstoff-Atomen substituiert sein kann.

5. Verbindung nach Anspruch 1, worin R^1 ein aromatisch-aliphatischer K hl nwasserstoff-Rest, in aromatischer Kohlenwasserstoff-Rest oder eine heteroaromatische Ring-Gruppe ist, die jeweils durch ein Halogen, Hydroxyl, Cyano, Trifluoromethyl, Alkoxy mit 1 bis 4 Kohlenstoff-Atomen, Alkyl mit 1 bis 4 Kohlenst ff-At m n, Alkoxycarb nyl mit 2 bis 4 Kohlenstoff-Atomen oder Alkylthi mit 1 bis 3 Kohlenstoff-At m n substituiert sein kann.

6. Verbindung nach Anspruch 1, worin R^2 ein Alkyl mit 1 bis 5 Kohlenstoff-Atomen ist.

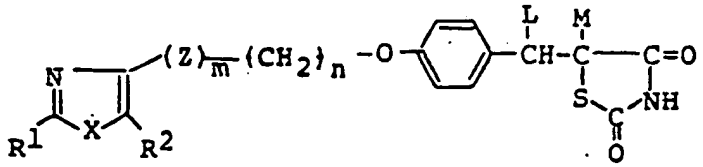
7. Verbindung nach Anspruch 1, worin m 1 ist und Z Hydr xymethylen ist.

8. Verbindung nach Anspruch 1, worin die Verbindung 5-{4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyliden}-2,4-thiazolidindion ist.

9. Verbindung nach Anspruch 1, worin die Verbindung 5-{4-[2-(5-Methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-2,4-thiazolidindion ist.

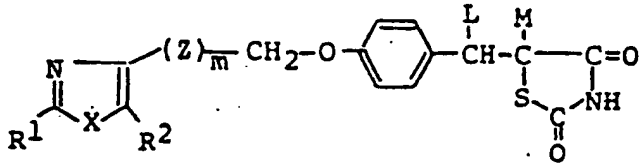
10. Verbindung nach Anspruch 1, worin die Verbindung 5-{4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-thiazolidindion ist.

11. Pharmazeutische Zusammensetzung, enthaltend ein Thiazolidindion-Derivat der allgemeinen Formel

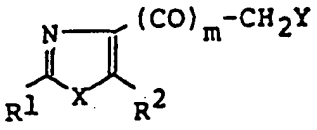


wie sie in Anspruch 1 definiert ist, oder ein pharmazeutisch annehmbares Salz derselben.

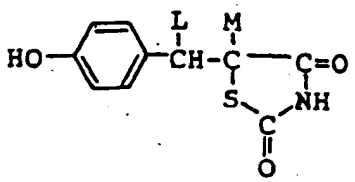
12. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel



worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben, oder eines Salzes derselben, umfassend die Umsetzung einer Verbindung der allgemeinen Formel

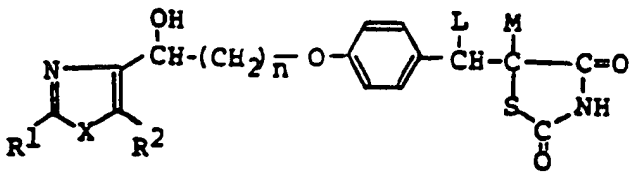


[in der Y ein Halogen-Atom ist und die anderen Symbole die in Anspruch 1 angegebenen Bedeutungen haben] mit einer Verbindung der allgemeinen Formel

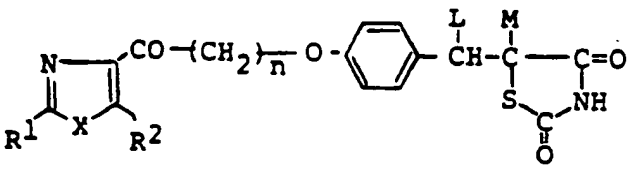


[in der L und M die in Anspruch 1 angegebenen Bedeutungen haben] oder einem Salz derselben, und nachfolgend, falls gewünscht, die Reduktion des Reaktionsprodukts.

13. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel

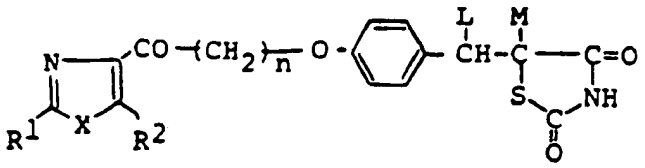


worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben, oder eines Salzes derselben, umfassend die Reduktion einer Verbindung der allgemeinen Formel

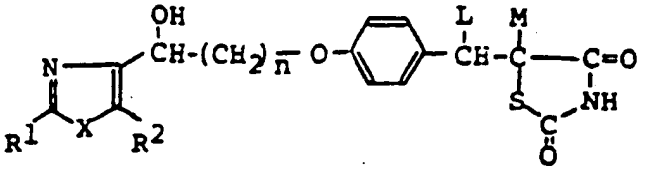


[in der sämtliche Symbole die in Anspruch 1 angegebenen Bedeutungen haben] oder eines Salzes ders lben.

14. Verfahren zur Herstellung einer Verbindung der allgem inen F rmel

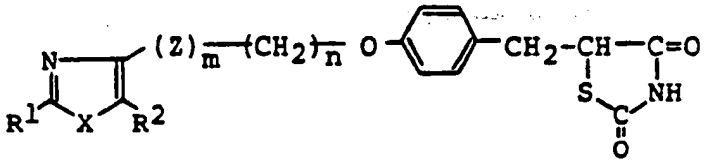


worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben, oder eines Salzes derselben, umfassend die Oxidation einer Verbindung der allgemeinen Formel

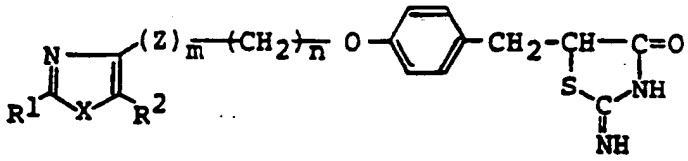


[in der sämtliche Symbole die in Anspruch 1 angegebenen Bedeutungen haben] oder eines Salzes derselben.

15. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel

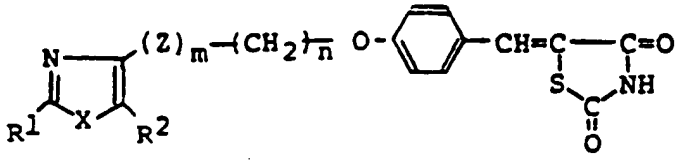


worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben, oder eines Salzes derselben, umfassend die Hydrolyse einer Verbindung der allgemeinen Formel

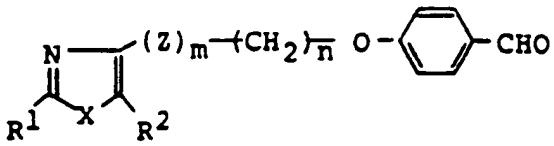


[in der sämtliche Symbole die in Anspruch 1 angegebenen Bedeutungen haben] oder eines Salzes derselben.

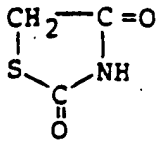
16. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel



worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben, oder eines Salzes derselben, umfassend die Umsetzung einer Verbindung der allgemeinen Formel

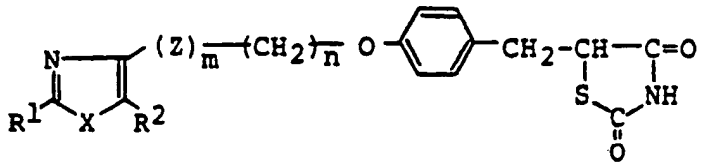


[in der sämtliche Symbole die in Anspruch 1 angegebenen Bedeutungen haben] mit einer Verbindung der Formel

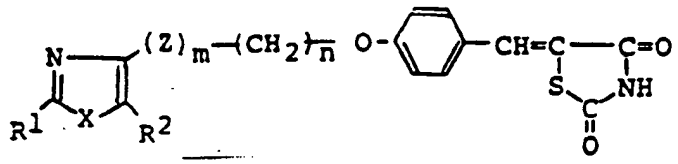


oder deren Salz.

17. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel



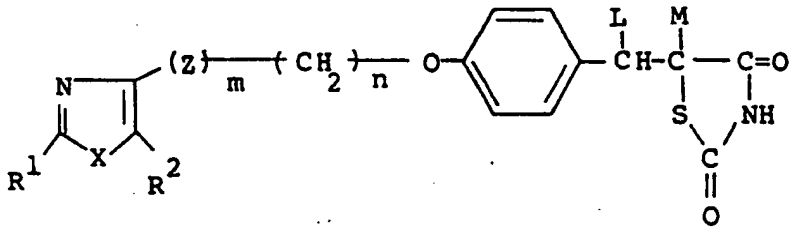
worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben, oder eines Salzes derselben, umfassend die Reduktion einer Verbindung der allgemeinen Formel



[in der sämtliche Symbole die in Anspruch 1 angegebenen Bedeutungen haben].

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel



worin

R^1 Wasserstoff, ein Kohlenwasserstoff-Rest mit 1 bis 13 Kohlenstoff-Atomen oder ein fünf- oder sechsgliedriger Ring ist, der neben Kohlenstoff 1 bis 3 aus N, O und S ausgewählte Atome als ringbildendes Atom enthält und zur Bindung über Kohlenstoff befähigt ist, und der Kohlenwasserstoff-Rest und der Ring jeweils durch 1 bis 3 Substituenten, die aus Alkyl mit 1 bis 3 Kohlenstoff-Atomen ausgewählt sind, wenn R^1 eine alicyclische Gruppe enthält oder eine gesättigte heterocyclische Gruppe ist, oder durch 1 bis 4 Substituenten, die aus Halogen, Hydroxyl, Cyano, Trifluoromethyl, Alkoxy mit 1 bis 4 Kohlenstoff-Atomen, Alkyl mit 1 bis 4 Kohlenstoff-Atomen, Alkoxycarbonyl mit 2 bis 4 Kohlenstoff-Atomen und Alkylthio mit 1 bis 3 Kohlenstoff-Atomen ausgewählt sind, wenn R^1 entweder einen aromatischen Kohlenwasserstoff umfaßt oder R^1 eine heteroaromatische Ring-Gruppe ist;
substituiert sein können,

R^2 Wasserstoff oder Niederalkyl mit 1 bis 5 Kohlenstoff-Atomen, das durch Hydroxyl substituiert sein kann, ist;

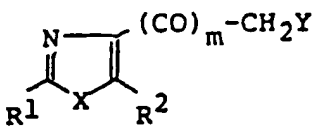
X ein Sauerstoff- oder Schwefel-Atom ist;

Z ein hydroxyliertes Methylen oder Carbonyl ist;

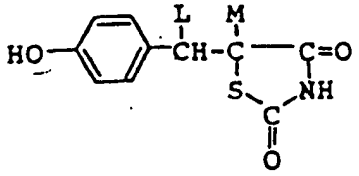
m 0 oder 1 ist;

L und M unabhängig voneinander ein Wasserstoff-Atom darstellen oder so miteinander kombiniert sind, daß sie gemeinsam eine Bindung bilden,

oder eines Salzes derselben, umfassend die Umsetzung einer Verbindung der allgemeinen Formel

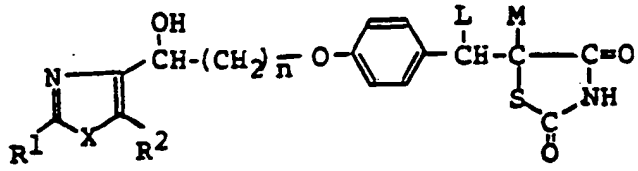


[in der Y ein Halogen-Atom ist und die anderen Symbole die im Vorstehenden angegebenen Bedeutungen haben] mit einer Verbindung der allgemeinen Formel

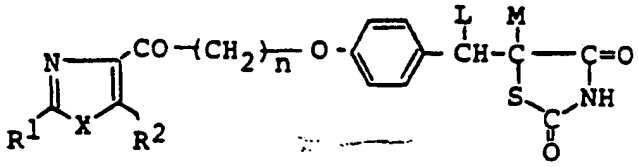


[in der L und M die in Anspruch 1 angegebenen Bedeutungen haben] oder einem Salz derselben, und nachfolgend, falls gewünscht, die Reduktion des Reaktionsprodukts.

2. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel

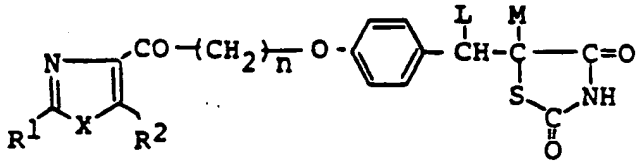


worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben und n eine ganze Zahl von 1 bis 3 ist, oder eines Salzes derselben, umfassend die Reduktion einer Verbindung der allgemeinen Formel

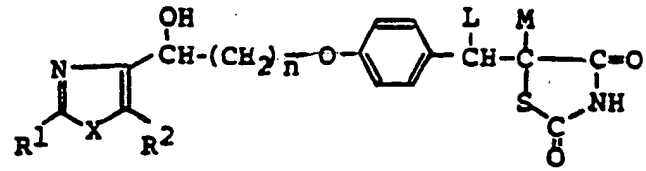


[in der sämtliche Symbole die in Anspruch 1 angegebenen Bedeutungen haben] oder eines Salzes derselben.

3. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel

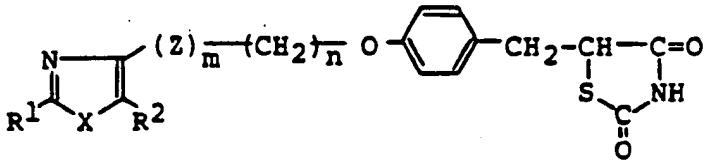


worin die Symbole die in Anspruch 2 angegebenen Bedeutungen haben, oder eines Salzes derselben, umfassend die Oxidation einer Verbindung der allgemeinen Formel

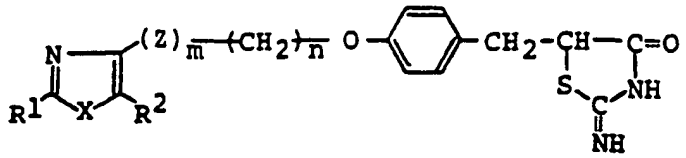


[in der sämtliche Symbole die in Anspruch 1 angegebenen Bedeutungen haben] oder eines Salzes derselben.

4. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel

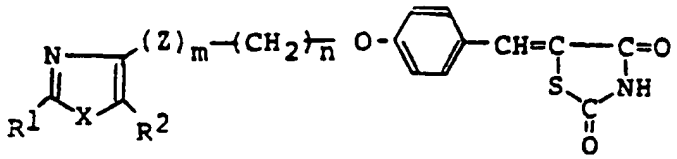


worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben und n eine ganze Zahl von 1 bis 3 ist, oder eines Salzes derselben, umfassend die Hydrolyse einer Verbindung der allgemeinen Formel

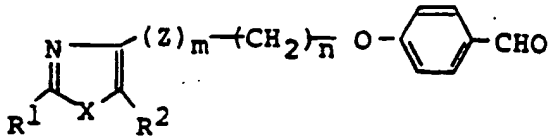


[in der sämtliche Symbole die in Anspruch 1 angegebenen Bedeutungen haben] oder eines Salzes derselben.

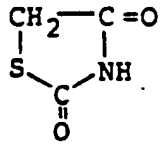
5. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel



worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben und n eine ganze Zahl von 1 bis 3 ist, oder eines Salzes derselben, umfassend die Umsetzung einer Verbindung der allgemeinen Formel

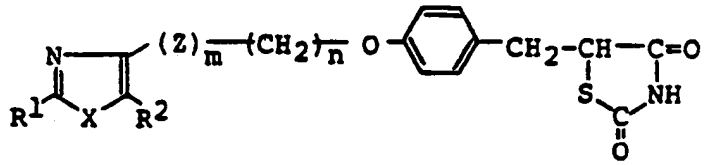


[in der sämtliche Symbole die in Anspruch 1 angegebenen Bedeutungen haben] mit einer Verbindung der Formel

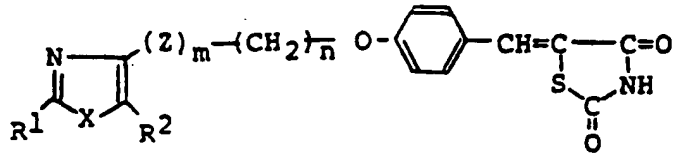


oder deren Salz.

6. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel



worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben und n eine ganze Zahl von 1 bis 3 ist, oder eines Salzes derselben, umfassend die Reduktion einer Verbindung der allgemeinen Formel



[in der sämtliche Symbole die in Anspruch 1 angegebenen Bedeutungen haben].

7. Verfahren nach irgendeinem der Ansprüche 1 bis 6, worin der durch R^1 dargestellte Kohlenwasserstoff-Rest ein aliphatischer Kohlenwasserstoff-Rest, ein alicyclischer Kohlenwasserstoff-Rest, ein alicyclisch-aliphatischer Kohlenwasserstoff-Rest, ein aromatisch-aliphatischer Kohlenwasserstoff-Rest oder ein aromatischer Kohlenwasserstoff-Rest ist.

8. Verfahren nach irgendeinem der Ansprüche 1 bis 7, worin der heterocyclische Rest eine heteroaromatische Ring-Gruppe oder eine gesättigte heterocyclische Gruppe ist.

9. Verfahren nach irgendeinem der Ansprüche 1 bis 8, worin R^1 ein alicyclischer Kohlenwasserstoff-Rest, in alicyclisch-aliphatischer Kohlenwasserstoff-Rest der eine gesättigte heterocyclische Gruppe ist, die jeweils durch ein Niederalkyl mit 1 bis 3 Kohlenstoff-Atomen substituiert sein kann.

10. Verfahren nach irgendeinem der Ansprüche 1 bis 9, worin R^1 ein aromatisch-aliphatischer Kohlenwasserstoff-Rest, ein aromatischer Kohlenwasserstoff-Rest oder eine heteroaromatische Ring-

Gruppe ist, die jeweils durch ein Halogen, Hydroxyl, Cyano, Trifluoromethyl, Alk xy mit 1 bis 4 K hlenstoff-Atomen, Alkyl mit 1 bis 4 Kohlenstoff-Atomen, Alkoxycarb nyl mit 2 bis 4 Kohlenstoff-Atomen der Alkylthi mit 1 bis 3 Kohlenstoff-Atomen substituiert sein kann.

11. Verfahren nach irgendeinem der Ansprüche 1 bis 10, worin R^2 ein Alkyl mit 1 bis 5 Kohlenstoff-Atomen ist.

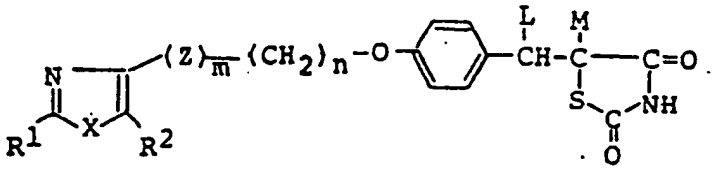
12. Verfahren nach irgendeinem der Ansprüche 1 bis 11, worin m 1 ist und Z Hydroxymethylen ist.

13. Verfahren nach Anspruch 1, worin die Verbindung 5-{4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyliden}-2,4-thiazolidindion ist.

14. Verfahren nach Anspruch 1, worin die Verbindung 5-{4-[2-(5-Methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-2,4-thiazolidindion ist.

15. Verfahren nach Anspruch 1, worin die Verbindung 5-{4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl}-2,4-thiazolidindion ist.

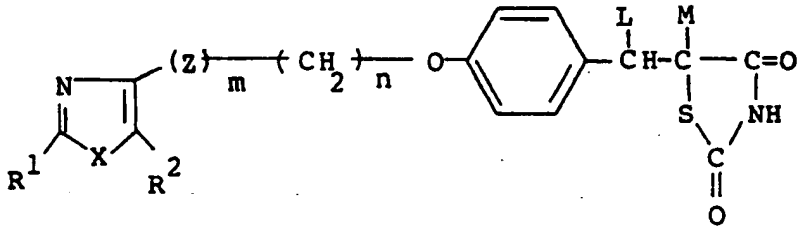
16. Pharmazeutische Zusammensetzung, enthaltend ein Thiazolidindion-Derivat der allgemeinen Formel



worin die Symbole die in Anspruch 1 angegebenen Bedeutungen haben und n eine ganze Zahl von 1 bis 3 ist, oder ein pharmazeutisch annehmbares Salz derselben.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composé de formule générale:



dans laquelle

R^1 est l'hydrogène, un radical hydrocarboné comportant de 1 à 13 atomes de carbone ou un cycle à 5 ou 6 chaînons contenant, en plus du carbone, de 1 à 3 atomes choisis parmi N, O et S en tant qu'atomes formant un cycle et capables d'être attachés au carbone et ledit radical hydrocarboné ainsi que ledit cycle peuvent être substitués soit par 1 à 3 substituants choisis parmis les alcoyles comportant de 1 à 3 atomes de carbone, lorsque R^1 comprend un groupe alicyclique ou consiste en un groupe hétérocyclique saturé, soit par 1 à 4 substituants choisis parmi un halogène, hydroxyle, cyano, trifluorométhyle, alcoxy comportant de 1 à 4 atomes de carbone, alcoyle comportant de 1 à 4 atomes de carbone, alcoxycarbonyle comportant de 2 à 4 atomes de carbone et alcoylthio comportant de 1 à 3 atomes de carbone, lorsque R^1 comprend un hydrocarbure aromatique ou R^1 est un groupe cyclique hétéroaromatique;

R^2 est l'hydrogène ou un alcoyle inférieur comportant de 1 à 5 atomes de carbone, qui peut être substitué par un hydroxyle;

X est un atome d'oxygène ou de soufre;

Z est un méthylène hydroxylé ou un carbonyle;

m est 0 ou 1;

n est un nombre entier de 1 à 3;

L et M représentent, indépendamment, un atome d'hydrogène ou L et M pris l'un avec l'autre forment ensemble une liaison,

ou un sel pharmaceutiquement acceptable de ce composé.

2. Composé selon la revendication 1, dans lequel le radical hydrocarboné représenté par R^1 est un radical hydrocarboné aliphatique, un radical hydrocarboné alicyclique, un radical hydrocarboné alicyclique-aliphatique, un radical hydrocarboné aromatique-aliphatique ou un radical hydrocarboné aromatique.

3. Comp sé selon la revendication 1, dans lequel le radical hétérocyclique est un groupe cyclique hétér aromatique ou un groupe hétér cyclique saturé.

4. Composé selon la revendication 1, dans lequel R^1 est un radical hydrocarboné alicyclique, un radical hydr carb né alicyclique-aliphatique ou un groupe hétérocyclique saturé, chacun d'eux pouvant être substitué par un alcoyle inférieur comportant de 1 à 3 atomes de carb ne.

5. Composé selon la revendication 1, dans lequel R^1 est un radical hydrocarboné aromatique-aliphatique, un radical hydrocarboné aromatique ou un groupe cyclique hétéroaromatique, chacun d'eux pouvant être substitué par un halogène, hydroxyle, cyano, trifluorométhyle, un alcoxy comportant de 1 à 4 atomes de carbone, un alcoyle comportant de 1 à 4 atomes de carbone, un alcoxycarbonyle comportant de 2 à 4 atomes de carbone ou un alcoylthio comportant de 1 à 3 atomes de carbone.

6. Composé selon la revendication 1, dans lequel R^2 est un alcoyle comportant de 1 à 5 atomes de carbone.

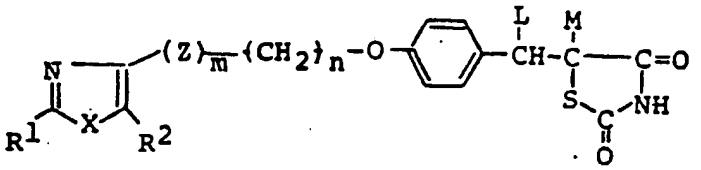
7. Composé selon la revendication 1, dans lequel m est 1 et Z est un hydroxyméthylène.

8. Composé selon la revendication 1, qui est la 5-(4-(2-(5-méthyl-2-phényl-4-oxazolyl)éthoxy)benzylidène)-2,4-thiazolidine dione.

9. Composé selon la revendication 1, qui est la 5-(4-(2-(5-méthyl-2-phényl-4-oxazolyl)-2-hydroxyéthoxy)benzyl)-2,4-thiazolidine dione.

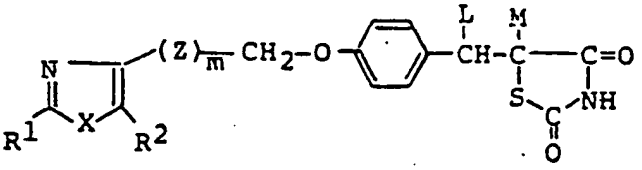
10. Composé selon la revendication 1, qui est la 5-(4-(2-(5-méthyl-2-phényl-4-oxazolyl)éthoxy)benzyl)-2,4-thiazolidine dione.

11. Composition pharmaceutique qui contient un dérivé de thiazolidine dione de formule générale:

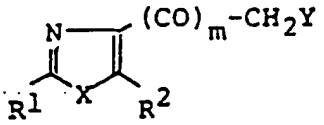


telle que défini à la revendication 1, ou un sel pharmaceutiquement acceptable de ce composé.

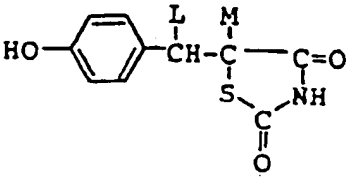
12. Procédé de préparation d'un composé de formule générale:



dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend la réaction d'un composé de formule générale:

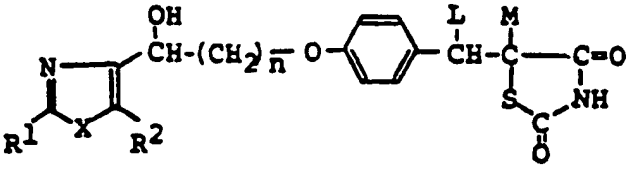


dans laquelle Y est un atome d'halogène et les autres symboles sont tels que défini à la revendication 1, avec un composé de formule générale:

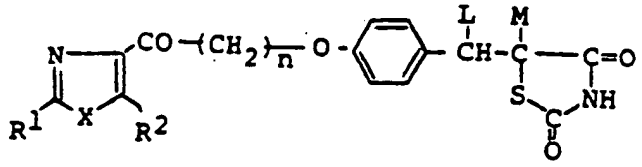


dans laquelle L et M sont tels que défini à la revendication 1, ou avec un sel de celui-ci, suivie, si désiré, de la réduction du produit réactionnel.

13. Procédé de préparation d'un composé de formule générale:

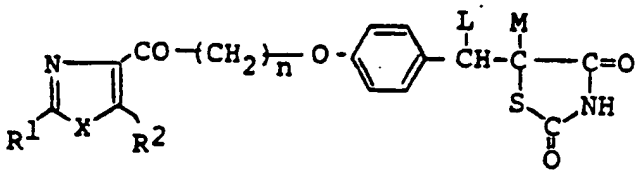


dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend la réduction d'un composé de formule générale:

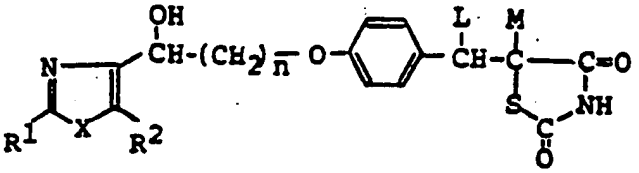


dans laquelle chacun des symboles est tel que défini à la revendication 1, ou d'un sel de celui-ci.

14. Procédé de préparation d'un composé de formule générale:

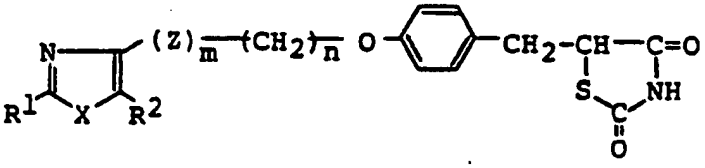


dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend l'oxydation d'un composé de formule générale:

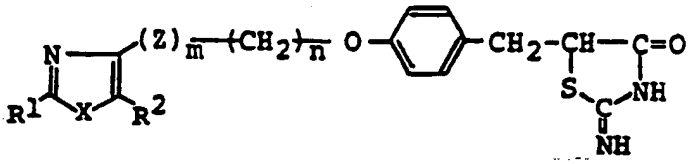


dans laquelle chacun des symboles est tel que défini à la revendication 1, ou d'un sel de celui-ci.

15. Procédé de préparation d'un composé de formule générale:

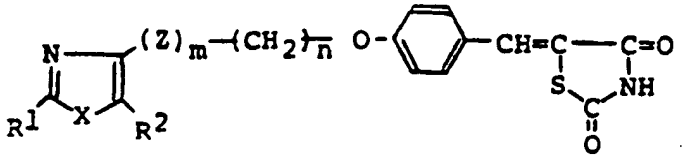


dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend l'hydrolyse d'un composé de formule générale:

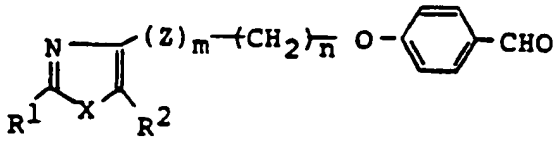


dans laquelle chacun des symboles est tel que défini à la revendication 1, ou d'un sel de celui-ci.

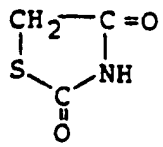
16. Procédé de préparation d'un composé de formule générale:



dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend la réaction d'un composé de formule générale:

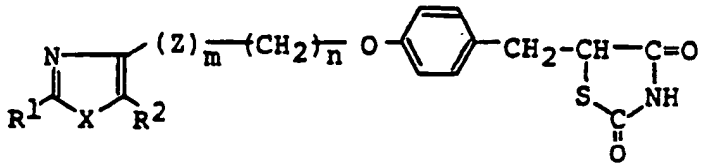


dans laquelle chacun des symboles est tel que défini à la revendication 1, avec un composé de formule:

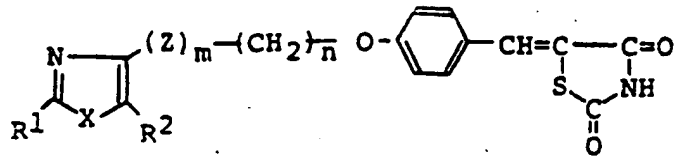


ou avec un sel de celui-ci.

17. Procédé de préparation d'un composé de formule générale:



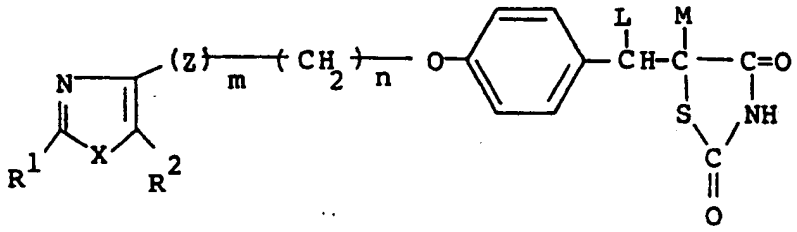
dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend la réduction d'un composé de formule générale:



dans laquelle chacun des symboles est tel que défini à la revendication 1.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule générale:



dans laquelle

R^1 est l'hydrogène, un radical hydrocarboné comportant de 1 à 13 atomes de carbone ou un cycle à 5 ou 6 chaînons contenant, en plus du carbone, de 1 à 3 atomes choisis parmi N, O et S en tant qu'atomes formant un cycle et capables d'être attachés au carbone et ledit radical hydrocarboné ainsi que ledit cycle peuvent être substitués soit par 1 à 3 substituants choisis parmis les alcoyles comportant de 1 à 3 atomes de carbone, lorsque R^1 comprend un groupe alicyclique ou consiste en un groupe hétérocyclique saturé, soit par 1 à 4 substituants choisis parmi un halogène, hydroxyle, cyano, trifluorométhyle, alcoxy comportant de 1 à 4 atomes de carbone, alcoyle comportant de 1 à 4 atomes de carbone, alcoxycarbonyle comportant de 2 à 4 atomes de carbone et alcoylthio comportant de 1 à 3 atomes de carbone, lorsque R^1 comprend un hydrocarbure aromatique ou R^1 est un groupe cyclique hétéroaromatique;

R^2 est l'hydrogène ou un alcoyle inférieur comportant de 1 à 5 atomes de carbone, qui peut être substitué par un hydroxyle;

X est un atome d'oxygène ou de soufre;

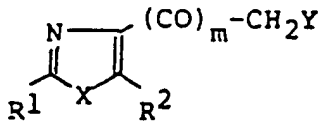
Z est un méthylène hydroxylé ou un carbonyle;

m est 0 ou 1;

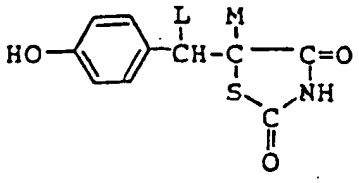
n est un nombre entier de 1 à 3;

L et M représentent, indépendamment, un atome d'hydrogène ou L et M pris l'un avec l'autre forment ensemble une liaison,

ou d'un sel de celui-ci, qui comprend la réaction d'un composé de formule générale:

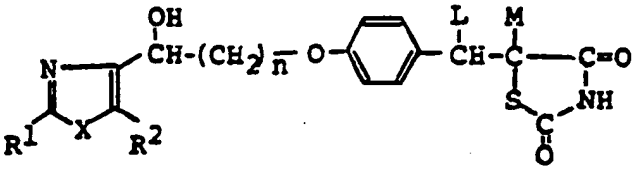


dans laquelle Y est un atome d'halogène et les autres symboles sont tels que défini à la revendication 1, avec un composé de formule générale:

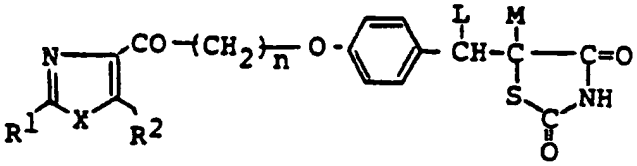


dans laquelle L et M sont tels que défini à la revendication 1, ou avec un sel de celui-ci, suivie, si désiré, de la réduction du produit réactionnel.

2. Procédé de préparation d'un composé de formule générale:

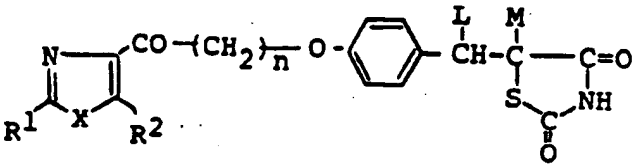


dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend la réduction d'un composé de formule générale:

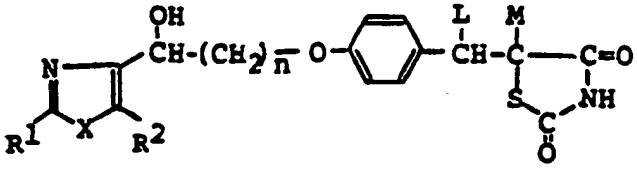


dans laquelle chacun des symboles est tel que défini à la revendication 1, ou d'un sel de celui-ci.

3. Procédé de préparation d'un composé de formule générale:

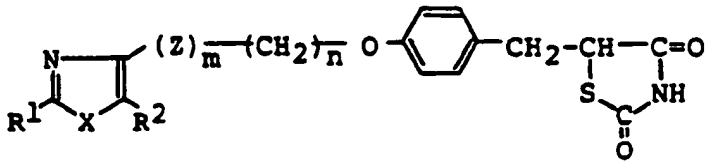


dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend l'oxydation d'un composé de formule générale:

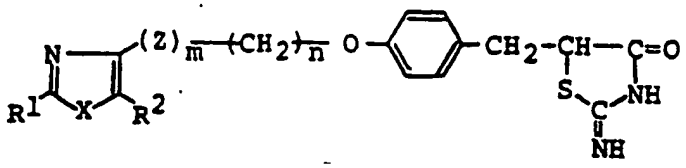


dans laquelle chacun des symboles est tel que défini à la revendication 1, ou d'un sel de celui-ci.

4. Procédé de préparation d'un composé de formule générale:

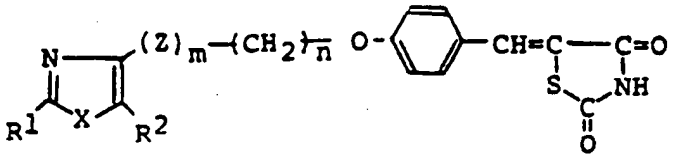


dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend l'hydrolyse d'un composé de formule générale:

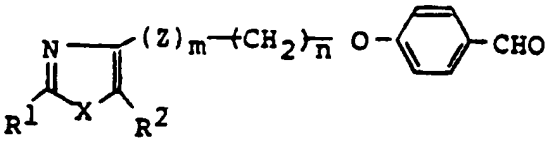


dans laquelle chacun des symboles est tel que défini à la revendication 1, ou d'un sel de celui-ci.

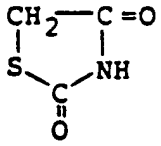
5. Procédé de préparation d'un composé de formule générale:



dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend la réaction d'un composé de formule générale:

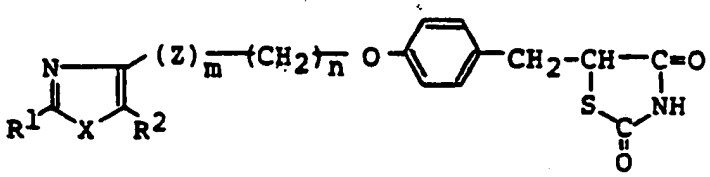


dans laquelle chacun des symboles est tel que défini à la revendication 1, avec un composé de formule:

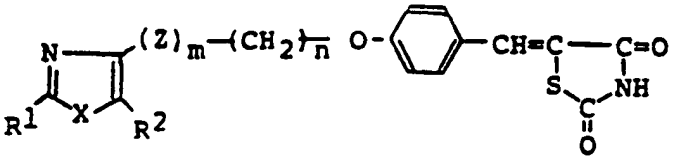


ou avec un sel de celui-ci.

6. Procédé de préparation d'un composé de formule générale:



dans laquelle les symboles sont tels que défini à la revendication 1, ou d'un sel de celui-ci, qui comprend la réduction d'un composé de formule générale:



dans laquelle chacun des symboles est tel que défini à la revendication 1.

7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel le radical hydrocarboné représenté par R^1 est un radical hydrocarboné aliphatique, un radical hydrocarboné alicyclique, un radical hydrocarboné alicyclique-aliphatique, un radical hydrocarboné aromatique-aliphatique ou un radical hydrocarboné aromatique.

8. Procédé selon l'une quelconque des revendicati ns 1 à 7, dans lequel le radical hétérocyclique est un groupe cyclique hétéroaromatique ou un group hétérocyclique saturé.

9. Procédé selon l'un quelconque des revendicati ns 1 à 8, dans lequel R^1 est un radical hydrocarb né alicyclique, un radical hydr carboné alicyclique-aliphatique ou un groupe hétérocyclique saturé, chacun d'eux pouvant êtr substitué par un alcoyl inférieur c mportant d 1 à 3 at m s d carb ne.

10. Procédé selon l'une quelc nque des revendicati ns 1 à 9, dans lequel R^1 est un radical hydrocarboné aromatique-aliphatique, un radical hydrocarb né aromatique ou un groupe cyclique

hétéroaromatique, chacun d'eux pouvant être substitué par un halogène, hydroxyle, cyano, trifluorométhyle, un alcoxy comportant de 1 à 4 atomes de carbone, un alcoyle comportant de 1 à 4 atomes de carbone, un alcoxycarbonyle comportant de 2 à 4 atomes de carbone ou un alcoylthio comportant de 1 à 3 atomes de carbone.

11. Procédé selon l'une quelconque des revendications 1 à 10, dans lequel R^2 est un alcoyle comportant de 1 à 5 atomes de carbone.

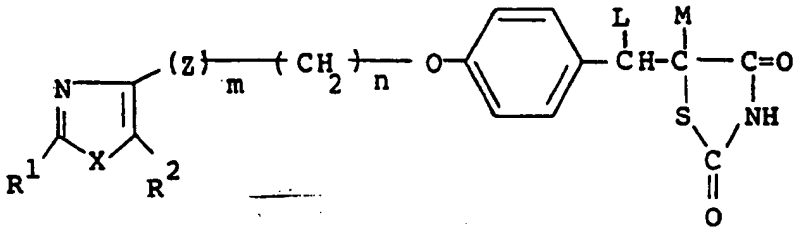
12. Procédé selon l'une quelconque des revendications 1 à 11, dans lequel m est 1 et Z est un hydroxyméthylène.

13. Procédé selon la revendication 1, dans lequel le composé obtenu est la 5-(4-(2-(5-méthyl-2-phényl-4-oxazolyl)éthoxy)benzylidène)-2,4-thiazolidine dione.

14. Procédé selon la revendication 1, dans lequel le composé obtenu est la 5-(4-(2-(5-méthyl-2-phényl-4-oxazolyl)-2-hydroxyéthoxy)-benzyl)-2,4-thiazolidine dione.

15. Procédé selon la revendication 1, dans lequel le composé obtenu est la 5-(4-(2-(5-méthyl-2-phényl-4-oxazolyl)éthoxy)benzyl)-2,4-thiazolidine dione.

16. Composition pharmaceutique qui contient un dérivé de thiazolidine dione de formule générale:



telle que défini à la revendication 1, ou un sel pharmaceutiquement acceptable de ce composé.